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Molecular Mechanism of Black Tea (Camellia sinensis) as SARS-CoV-2 Spike Glycoprotein Inhibitor through Computational Approach

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ABSTRACT
SARS-CoV-2 infection in humans also causes cytokine storm and can lead to patient death, this condition occurs due to the excessive release of pro-inflammatory cytokines by immune cells. SARS-CoV-2 infects cells in the human respiratory tract. Spike glycoprotein aims to bind to ACE2 in the viral entry process. Several studies have suggested that the SARS-CoV-2 spike is an ideal target for drug design. Camellia sinensis or black tea is a member of the Theaceae family and the genus Camellia. Camellia is a vast genus to East India, the Malay Peninsula, and Southeast Asia, together with Indonesia. In truth, Camellia sinensis is a tropical fruit that has been used as a traditional medicine for hundreds of years globally. This study is to identify the bioactive compounds from Camellia sinensis as an antiviral agent via spike glycoprotein inhibitor mechanisms against the SARS-CoV-2 infection through the in silico approach.

Keywords: Antiviral, Bioinformatics, Camellia sinensis, SARS-CoV-2

INTRODUCTION

SARS-CoV-2 infection in humans also causes cytokine storm and can lead to patient death, this condition occurs due to the excessive release of pro-inflammatory cytokines by immune cells[1]. SARS-CoV-2 infects cells in the human respiratory tract. The status of the presence of effective antivirals used to treat SARS-CoV-2 infection in patients is also very minimal or there is not enough information The virus binds to the host cell through a RBD in the S1 domain of the spike protein with ACE-2. In addition, SARS-CoV-2 can stimulate increased secretion of pro-inflammatory cytokines IL-6, TNF-α, and IL-1β through the activation of NFκB/NFKB1[2]. NFKB1 is the key to the activity of pro-inflammatory cytokines released by

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the immune system when a cytokine storm occurs. Spike glycoprotein aims to bind to ACE2 in the viral entry process[3]. Several studies have suggested that the SARS-CoV-2 spike is an ideal target for drug design.

Indonesia additionally is a nation which enriched in biodiversity, there are roughly 40,000 plant species, of which around 7,500 are medicinal plants, whether native or introduced species, cultivated or wild[4]. For ages, their worth has been recognized over the world for use as medications and cosmetics, as well as in traditional and modern applications. *Camellia sinensis* or black tea is a member of the Theaceae family and the genus Camellia. Camellia is a vast genus to East India, the Malay Peninsula, and Southeast Asia, together with Indonesia. In truth, *Camellia sinensis* is a tropical fruit that has been used as a traditional medicine for hundreds of years globally[5].

Many researchers reported antiviral activity of *Camellia sinensis* compound against chikungunya virus (CHIKV), porcine reproductive and respiratory syndrome virus (PRRSV), dengue virus (DENV), HIV-1, Influenza and avian pox virus[1,2,3]. Therefore, the aims of this study is to identify the bioactive compounds from *Camellia sinensis* as an antiviral agent via spike glycoprotein inhibitor mechanisms against the SARS-CoV-2 infection through the in silico approach.

METHODS

Sample preparation

The bioactive compound Camellia sinensis consists of Theaflavin, Theaflavin-3-3-digallate, Theaflavin-3-gallate, Theanine, Theobromine, and Theanine obtained from the PubChem database (*https://pubchem.ncbi.nlm.nih.gov/*)[5]. This study used spike glycoprotein of SARS-CoV-2 (PDB ID: 7KJ2) obtained from the protein databank (*https://www.rcsb.org/*). The ligand conversion process from sdf format to pdb was carried out using PyRx 0.9.9 version software and PyMol 2.5 version is used to remove water molecules in proteins[6].

Docking analysis

This simulation is to identify the ability of molecular interaction between ligand-protein and refers to the value of binding affinity[7]. This study used a docking screening method to determine potential domains in proteins for ligand binding targets. PyRx 0.9.9 version software was used in this study to simulate the docking of Camellia sinensis compound with spike glycoprotein of SARS-CoV-2. The position of the docking grid in this study was set to cover the entire protein surface[8].

Ligan-protein interaction

Weak bonds play a role in ligands to produce an activity response to proteins. The ligand-protein interactions formed are weak bonds, weak bonds such as hydrogen, electrostatic, alkyl, van der Waals, and hydrophobic[9]. The Discovery Studio 2016 software version was used in this study to identify the weak bonds formed in molecular complexes. Weak chemical bonds also affect of the ligand binding affinity value when it binds to the target domain[10].

Structural visualization

Molecular visualization of the ligand-protein complex was carried out using PyMol 2.3 version software through structural selection methods. The 3D structure shown consists of cartoons, surfaces, and sticks, staining is done on the protein chains and atoms of the ligand[11,12].

RESULT AND DISCUSSIONS

Binding affinity comparison of Black Tea (*Camellia sinensis*) compounds

Camellia sinensis is used for traditional medicine such as anti-inflammatory, antiviral, preventing free radicals, and others[13,14]. *Camellia sinensis* was identified to have chemical compounds consisting of Theaflavin, Theaflavin-3-3-digallate, Theaflavin-3-gallate, Theanine, Theobromine, and Theanine. This study used a chemical compound from *Camellia sinensis*. to identify candidate antiviral drugs against SARS-CoV-2 by inhibiting the activity of spike glycoprotein by molecular docking with grid position Center (Å) X:212.132 Y:183.703

Z:198.156, Dimensions (Å) X:132.535 Y:40.908 Z:147.047. Theaflavin-3-3-digallate has a binding affinity of -9.4 kcal/mol more negative than other compounds when it binds to SARS-CoV-2 spike protein (Table 1), Theaflavin-3-3-Digallate is predicted to inhibit the activity of spike because it has more negative binding than other compounds. The molecular docking simulation aims to determine the activity of the ligand binding on the protein domain by referring to the binding affinity value[15,16, 29]. The binding affinity value indicates the inhibitory ability of a ligand on the activity of the target protein[17,18,19]. Visualization of docking results is displayed through transparent surfaces structure and sticks (Figure 1).

Table 1. Binding affinity comparison

Compounds	CID	Molecular Weight (g/mol)	Target	Binding Affinity (kcal/mol)
Theaflavin	135403798	564.5	Spike	-9.0
Theaflavin-3-3-digallate	136277567	868.7	Spike	-9.4
Theaflavin-3-gallate	136825044	716.6	Spike	-9.1
Theanine	439378	174.2	Spike	-4.4
Theobromine	5429	180.16	Spike	-5.1
Theophylline	2153	180.16	Spike	-8.2

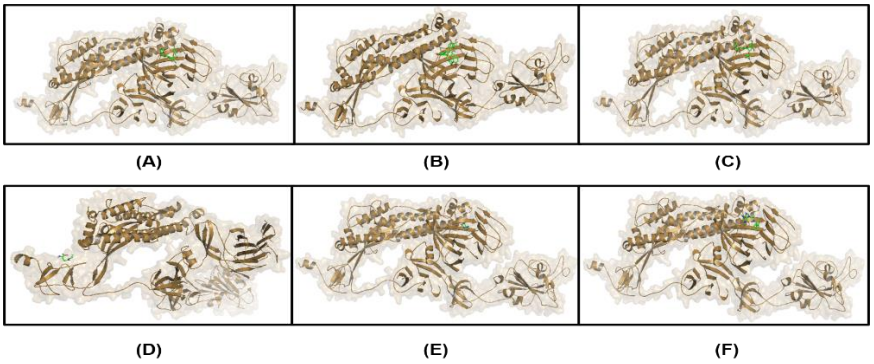

Figure 1. Visualization of the docking results. (A) Theaflavin (B) Theaflavin-3-3-digallate (C) Theaflavin-3-gallate (D) Theanine (E) Theobromine (F) Theophylline

Potential strategic pocket binding domain on SARS-CoV-2 spike glycoprotein

Chemical bond interactions in molecular complexes are identified to determine the type of bond and position[20,21,22]. Theaflavin-3-3-digallate have interaction position at Asn121, Arg190, Ile101, Ser205, Tyr170, His207, Arg102, Val126, Phe192, this position allows them to act as potential domains to lead inhibitory activity at E6 (Table 2). Weak bond interactions such as hydrogen and alkyl are also formed in all ligands, Theaflavin-3-3-digallate has more hydrogen bond interactions than other compounds and this can strengthen the prediction that Theaflavin-3-3-digallate can act as a good drug candidate. Weak bond interactions consisting of hydrogen, hydrophobic, and alkyl can play a role in triggering the response of biological activity on the target protein[23,24,25]. The number of hydrogen bonds can be used as an indicator of the stability of a drug candidate molecule[26,27,28]. Thus, Theaflavin-3-3-digallate is predicted to become a drug molecule because it can affect the activity of E6 protein through weak bonds and has the highest number

of hydrogen bonds. the visual results of molecular interactions in this study are displayed with a 2D structure (Figure 2).

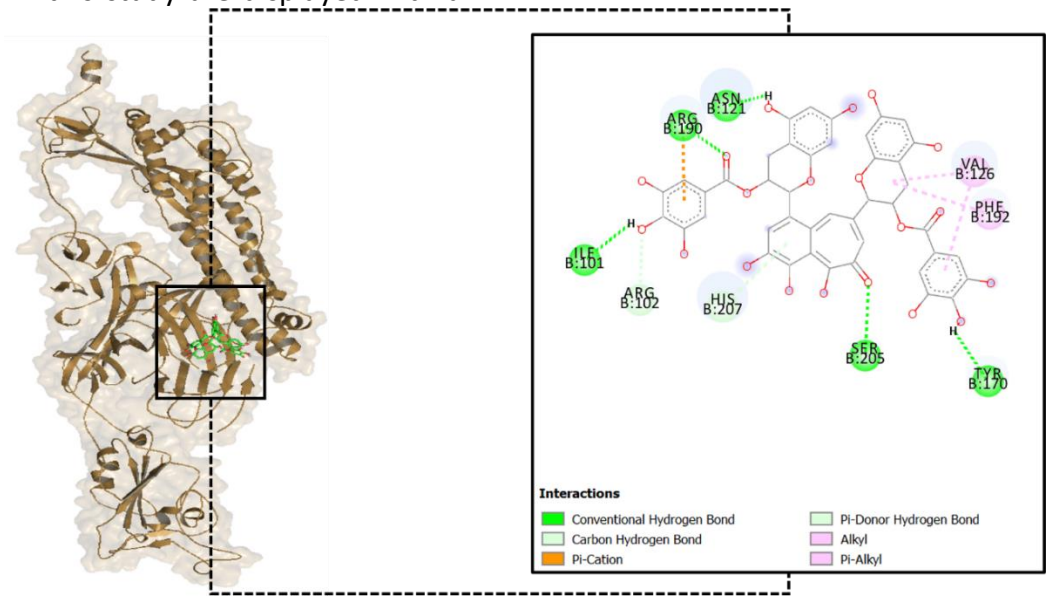

Figure 2. Molecular interactions on the Theaflavin-3-3-digallate_spike complex. Ligands are shown with green sticks and cartoons on proteins.

CONCLUSION

Black Tea (Cammellia sinensis) has the potential to be an antiviral for SARS-CoV-2 because it has Theaflavin-3-3-digallate with a more negative binding affinity and forms a weak bond consisting of hydrogen and alkyl, it can trigger the inhibition of the spike glycoprotein activity of SARS-CoV-2 and prevent the viral entry process. The results of this study must be re-examined through a wetlab approach to strengthen scientific evidence regarding the potential of Black tea (*Camellia sinensis*).

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