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Molecular Docking Analysis from *Bryophyllum pinnatum* Compound as A COVID-19 Cytokine Storm Therapy

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Abstract

BACKGROUND: Cytokine storm is a condition that typically develops during severe COVID-19 viral infection and contributes cause of death. *Bryophyllum pinnatum* is a herbal medicinal that has an impact as an anti-inflammatory agent. *B. pinnatum* may be used as a therapeutic agent for cytokine storms.

AIM: We were investigating the molecular interactions of *B. pinnatum* active compounds with cytokines involved in COVID-19 infection.

METHODS: We did the molecular docking approach using the active chemicals from *Bryphyllum pinnatum*, which was available on the PubChem website. Meanwhile, the protein utilized is retrieved from the protein databank. Pyrx 9.5, Pymol, and Discovery Studio software were used to evaluate and visualize the interaction results between ligands and the proteins formed.

RESULTS: Bryophyllin B has the strongest affinity to IL-6, whereas Bryotoxin A had the highest binding to Gly-ACE and TNF alpha. Pharmacokinetic predictions indicate that Bryophyllin B has a good pharmacokinetic profile but a low toxicity profile due to a reproductive effect. On the other hand, Bryotoxin A has a poor pharmacokinetic profile but is safe for human use.

CONCLUSIONS: Bryophyllin B and Bryotoxin A show potential as a therapy for the cytokine storm of COVID-19 infection. However, further study is required to examine the effectiveness and toxicity of these compounds.

Introduction

A novel member of the human coronavirus family, recently identified in Wuhan, China, and now formally recognized as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the International Committee on Taxonomy of Viruses (ICTV), is a novel strain of RNA viruses previously unknown in humans. From December 31, 2019 to the present, there have been 438 million cases, resulting in 5.91 million deaths. Indonesia itself currently has a total of 5.29 million cases and 147,000 deaths [1], [2].

Cytokine storm sometimes referred to as Cytokine Storm Syndrome (CSS) is a potentially provoked episode of Systemic Inflammatory Response Syndrome (SIRS). It arises as a result of the activation of a significant number of white blood cells, which generate pro-inflammatory cytokines. Recent studies of high serum cytokine levels in COVID-19 infection have association with the severe consequences associated with disease [3]. Pro-inflammatory cytokines of the innate immune response such as TNF-α and IL-6 are had the prior role of cytokine storm [3], [4]. These cytokines are produced by the endothelium, mast cells, tissue macrophages, and epithelial cells [5], [6].

Acute Respiratory Distress Syndrome (ARDS), which results in low oxygen saturation levels, is a significant cause of death by the increasing of pro-inflammatory cytokine production [6], [7]. A study showed that median levels of IL-6 in patients with COVID-19 are 6.98 pg/mL during pneumonia and ARDS. The survivors had a median level of IL-6 that is 6.3 pg/mL compared to 11 pg/mL in non-survivors [8]. It was a promising option to modulate the IL-6 for altered the disease progression to ARDS. Modulating IL-6 recently used for some inflammatory rheumatic diseases and hematologic malignancies [9]. Clinical manifestations of mild-to-moderate COVID-19 differ significantly according to the patient's age, gender, and presence of comorbid. Olfactory impairment is a sign of mild-to-moderate infection, but dyspnea and nausea are risk factors for more severe symptoms [10], [11].

The leaves extract of *Bryophyllum pinnatum* contains alkaloid chemicals, flavonoids, saponins, and tannins. *B. pinnatum*, which contains active substances such as Bryophyllin A, Bryophyllin B, Bryotoxin A,

and Bryotoxin B, was previously shown to have anti-inflammatory activity in experimental rats with systemic lupus erythematous (SLE) induced by pristine [12]. These chemicals were able to inhibit the production of TNF-α in SLE animals model [13]. There is no study that has been conducted on the anti-inflammatory impact of these active substances on cytokines involved in a cytokine storm.

We can forecast the capacity of compounds to interact with a target protein utilizing molecular docking studies. *In silico* is a technique that many researchers use to determine compounds that can be utilized as a drug against a certain target. This study serves as a foundation for determining the active substance of *B. pinnatum* as a therapy for cytokine storm in COVID-19 infection.

Materials and Methods

Ligands and protein preparation

Bryophyllin A, Bryophyllin B, Bryotoxin A, and Bryotoxin B were the active compound contained in *Bryophillum pinnatum* in our prior study [13]. We download the 3D chemical compounds sourced from the PubChem database [14]. The compounds were classified according to their ID, formula, canonical smile, and saved in sdf format. The samples IL-6, SARS-CoV-ACE2 glycoprotein complex (Glyc-ACE2), and TNFR (Tumor Necrosis Factor Receptor) were download from online protein database (RCSB) [15]. PyMol 2.5 was used to sterilize protein samples for molecular docking optimization and reduce each chemical obtained to increase its flexibility [16]. A personal computer with Windows 10 specifications, 16GB RAM, SSD 210, and Ryzen 5 2400U processor was used to increase the good quality docking process.

Pharmacokinetic profile analysis

To determine the pharmacokinetic profiles of the active compounds, SwissADME (http://www.swissadme.ch/index.php) was used, with the SMILES formula of each active compound entered as input. In addition, we utilized the OSIRIS website (https://www.organic-chemistry.org/prog/peo/) to evaluate the toxicity of each molecule in terms of potential dangers as well as mutagenicity [17], [18].

Ligands and protein interactions

The capacity of the ligands from *B. pinnatum* to bind to the targeted protein domain was determined in this work using molecular docking simulations. The purpose of molecular docking simulations was to ascertain the binding types when the ligand bound to the designated protein location, the binding energy generated by the ligand was able to initiate a particular biological reaction. The lowest binding score is the greatest biological activity [19], [20].

Visualization interaction

We assessed molecular binding complex interaction using the Discovery Studio program version 16.1.0. to determine the chemical interaction. Hydrogen, hydrophobic, electrostatic chemical, and Pi-Alkyl linkages were all visible in two-dimensional structures. PyMol was using to coloring and selection three-dimensional structure of the interaction result. The software framework was made out of sticks, cartoons, ribbons, spheres, and surfaces [19], [21].

Results and Discussion

To determine the intensity of the interaction between ligands and target proteins, the PyRx 9.5 program was employed. The prediction of bond strength was performed using a grid box with the following center coordinates and dimensions. Coordinate and dimension were used based on the prior COVID-19 study [19]. Coordinate and dimension for Gly-ACE were (X: 179.92, Y: 163.98, and Z: 124.42 and X: 43.31, Y: 25.00, and Z: 31.38), TNFR (X: 21.15, Y: 14.45, and Z: 35.67 and X: 25, Y:25, and Z:25), IL-6 (X: −0.20, Y: 0.30, and Z:0.29 and X: 25, Y:25, and Z:25). Bryophyllin A, Bryophyllin B, Bryotoxin A, and Bryotoxin B were obtained from Pubchem and provided with the following information: Identification number, weight, formula, and canonical smile (Table 1).

Table 1: Characteristics of samples containing the active compound *Bryophyllum pinnatum*

Compounds	Pubchem ID	Formula	Cannonical smile
Bryophyllin A	5488801	C26H32O8	CC12CC (C3C (C1(CCC2C4=COC(=O) C=C4) O) CCC56C3(C7CC (C5) OC (O7) (O6) C) C=O) O
Bryophyllin B	44575928	C26H34O9	CC(=O) OC1CC (CC2(C13C4C (CC2) C5(CCC (C5(CC4OC3O) C) C6=COC(=O) C=C6) O) O) O
Bryotoxin A	441848	C32H42O12	CC1CC (C(C (O1) OC2CCC3(C4C (CCC3(C2) O) C5(CCC (C5(C(=O) C4O) C) C6=COC(=O) C=C6) O) C=O) O) OC(=O) C
Bryotoxin B	5489391	C26H32O9	CC12C (CCC1(C3CCC45CC6CC (C4(C3C (C2=O) O) CO) OC (O6)(O5) C) O) C7=COC(=O) C=C7

The rule of 5 predicts that when there are more than five H-bond donors and ten H-bond acceptors, the molecular weight is larger than 500, and the estimated

Log P (CLog P) is greater than 5. Compounds that fulfill these requirements are considered to be drug-like and are suitable for oral administration [22]. According to the findings of the pharmacokinetic study of each compound, it was determined that Bryophyllin A, Bryophyllin B, and Bryotoxin B have good pharmacokinetics since they fulfill the Lipinski Rule of 5 criteria for oral administration and hence qualify as drugs. However, Bryotoxin A has poor pharmacokinetics properties, because it did not fulfill two of Lipinski's rules, mainly having an H acceptor greater than 10 and a molecular weight more than 500 g/mol (Table 2).

Table 2: Lipinski rule of five criteria

Compounds	Weight (g/mol)	Acceptor H	Donor H	Log P
Bryophyllin A	472.53	8	2	2.07
Bryophyllin B	490.54	9	4	1.24
Bryotoxin A	618.67	12	4	1.23
Bryotoxin B	488.3	9	3	1.46

In other hand, based on the OSIRIS toxicity prediction result, only Bryotoxin A has a high predictive value for medication safety because it is not mutagenic, tumorigenic, irritating, or affects reproductive organs. Bryophyllin A, Bryophyllin B, and Bryotoxin B had reproductive effect, so they were considered less safe to use (Table 3). However, further study is required to evaluate a compounds degree of safety for human.

Table 3: Toxicity risk of *Bryophyllum pinnatum* compounds

Compound	Mutagenic	Tumorigenic	Irritant	Reproductive effect
Bryophyllin A	1	1	1	0.8
Bryophyllin B	1	1	1	0.8
Bryotoxin A	1	1	1	1
Bryotoxin B	1	1	1	0.8

1: No risk, 0.8: Medium risk, 0.6: High risk.

Bryotoxin A had the strongest negative binding affinity, based on the results of the molecular docking simulation. This shows that Bryotoxin A was the most effective antiviral agent, as RBD cannot be connected to ACE. Meanwhile, comparison to the other compounds, Bryotoxin A was interacted with TNF-α receptor as the highest negative binding affinity. Beside, Bryotoxin A inhibited Gly-ACE and TNF-α receptors which have a function in generating cytokine storms. While, Bryophyllin B was able to decrease cytokine storms by inhibiting IL-6 activity with a strongest negative affinity. The binding affinity interaction is shown in Table 4.

Table 4: Binding affinity interaction ligands and protein target

Ligand	Binding affinity (Kcal/mol)		
	Glyc-Ace	IL-6	TNFR
Bryophyllin A	−6.4	−6.6	−4.1
Bryophyllin B	−6.2	−7.1	−3.2
Bryotoxin A	−6.6	−5.6	−5.6
Bryotoxin B	−6.4	−6.7	−1.5

IL-6: Interleukin 6, TNFR: Tumor necrosis factor receptor.

The inhibition interaction of a chemical and protein target can be seen by compared the bonds produced in the amino acid residue of interaction [23], [24]. According to the molecular interactions and binding positions analysis of docking protein-ligand complexes, the bindings of Bryotoxin A to ACE could create eight types of interactions, including Van der Waals, hydrogen, unfavorable interaction, and hydrophobic bonds (Figure 1). While, the interaction between Bryotoxin A molecules and the TNF receptor may produce three hydrophobic interactions (Figure 2). Bryophyllum B binds to IL-6 can generate a total of seven interactions, including hydrogen, Van der Waals, unfavorable, and pi bonds (Figure 3). The interaction of Gly-ACE in this study is the same as in other studies, with the exception of the creation of hydrogen bonds in Ser494 [19]. To trigger biological reactions in proteins, such as activation and inhibition, the type of interaction is crucial [25].

COVID-19 infection leads to inflammatory response and immune disturbance, which can lead to a wide range of different symptoms. COVID-19 may show up in different ways because of the cytokine storm [6]. In the case of cytokine storm, pro-inflammatory cytokines including IL-6 and TNF-α extremely elevated. The increasing of cytokines lead to migration of diverse immune cells such as T-cells, macrophages, neutrophils. It generates from the circulation into the infection site and can be a deleterious impact on human tissue due to endothelial cell instability [9]. Extensive alveolar damage, capillary injury, multiorgan failure, and death may result from extremely elevated cytokine-receptor interactions. A cytokine storm may cause lung damage, including acute lung injury (ALI) and ARDS [26].

Serum IL-6 levels are elevated in extremely in COVID-19 patients. Tocilizumab is an inhibitor of IL-6 that impairs the immune system's function. Tocilizumab mostly used in rheumatoid arthritis and other autoimmune diseases. Tocilizumab is a monoclonal antibody that has a therapeutic impact on the cytokine storm caused by infection. Clinical trials conducted in China have shown that Tocilizumab is beneficial in the treatment of critically sick patients who have significant bilateral lung lesions and increased IL-6 levels [27].

TNFs are critical pro-inflammatory cytokines that initiate a cytokine storm. They are interesting candidates for cytokine storm control. Anti-TNF medication dramatically enhanced survival in patients with sepsis [28]. In addition, anti-TNF medication has efficacy in the treatment of noninfectious illnesses such as atherosclerosis. TNF has been found in animal models to substantially contribute to acute lung damage and impede the T-cell response in SARS-CoV-infected mice. In mice, blocking TNF activity or deleting the TNF receptor protects against SARS-CoV-related morbidity and death [29].

Herbal plants may be used as an alternative medicine since they contain a variety of medicinal

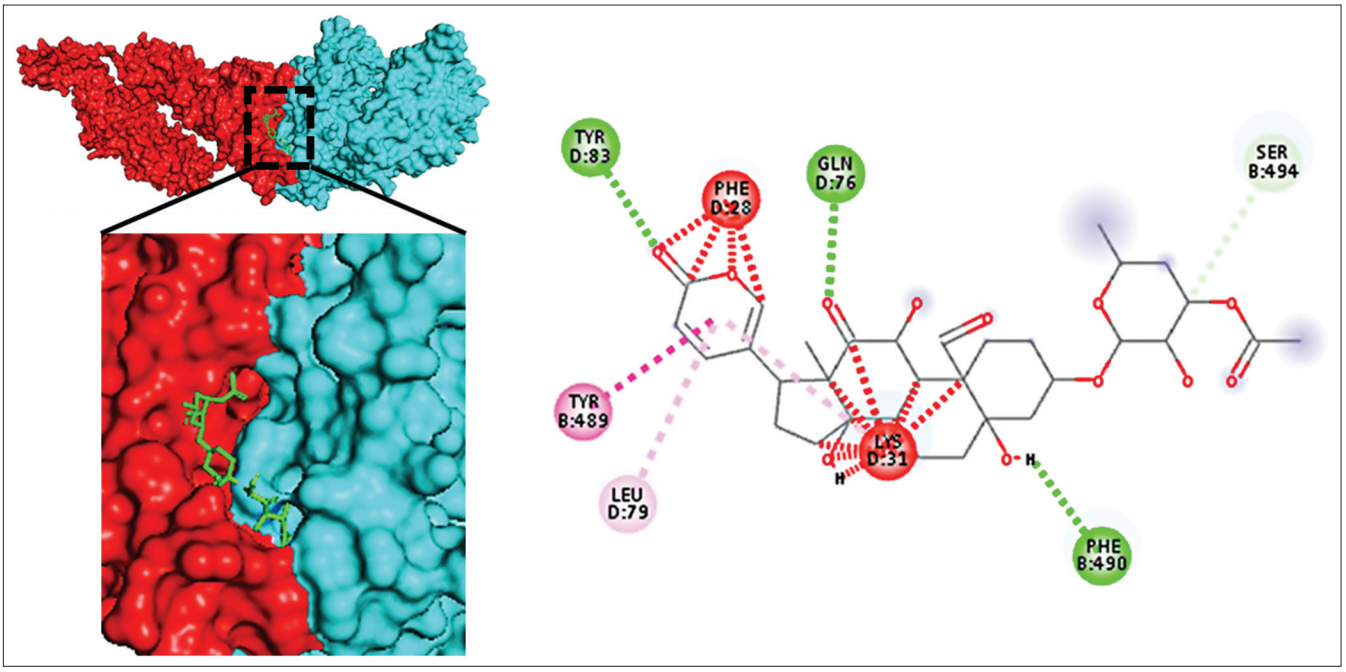

Figure 1: Gly-ACE protein with Bryotoxin A binding Interaction. ACE (Cyan), Glyc Spike COVID-19 (Red), Bryotoxin A (Green). Hydrogen Bond (Green Interaction), Hydrophobic Bond (Pink Interaction), unfavorable interaction (Red Interaction)

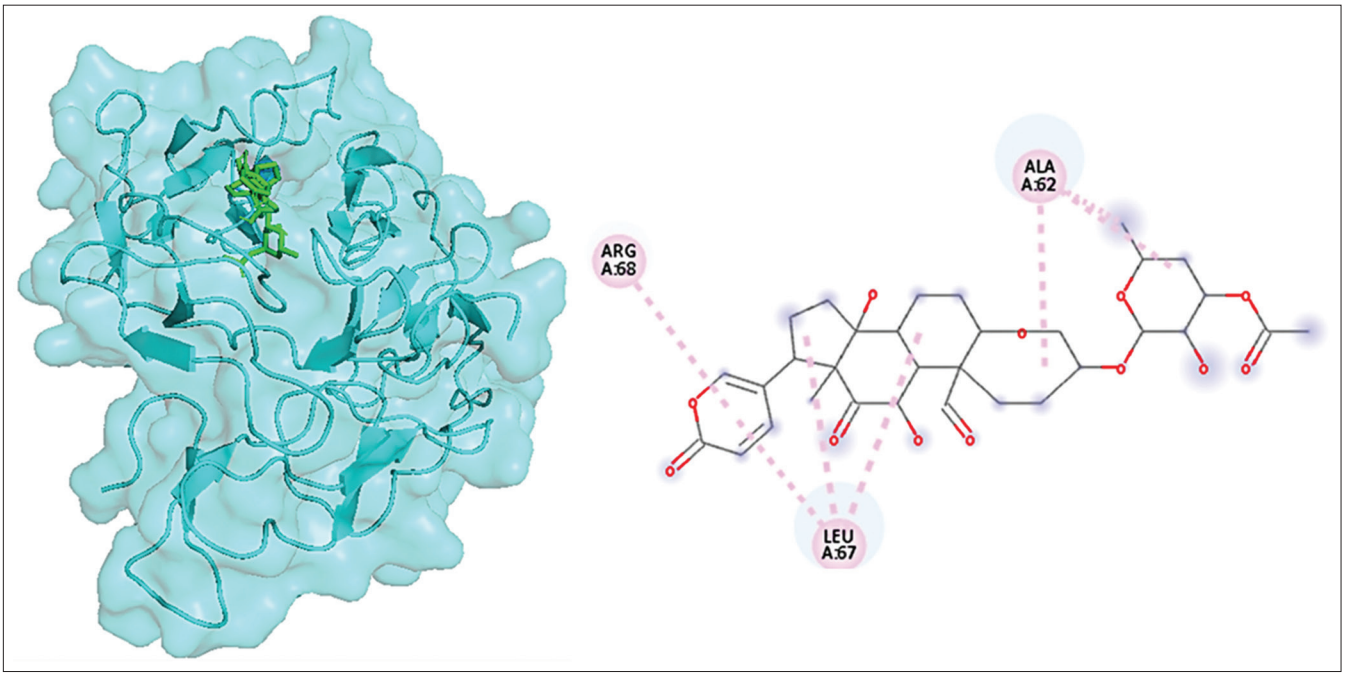

Figure 2: Interaction between Bryotoxin A and TNFR. Bryotoxin A (Green), Cyan (TNFR), Hydrophobic Bond (Pink Interaction)

compounds. Thus, drug candidate research will continue to be conducted to maximize the potential of nature. Bryophyllin B and Bryotoxin A are the most likely candidates for the active chemicals found in *B. pinnatum* in this study. Bryophyllin B and Bryotoxin A may operate as an immunoregulator in the treatment of SARS-CoV2 infection.

There is no particular anti-inflammatory research that has been conducted on Bryophyllin B and Bryotoxin A yet. Several studies have shown anti-inflammatory activity in the presence of *B. pinnatum* extract in mice [12], [13], [30]. In our result, the inflammatory action of the *B. pinnatum* plant caused by the presence of Bryophyllin B and Bryotoxin A.

The fundamental limitation is inadequate of confidence on the capabilities of scoring functions to give correct binding energies. The fact that some molecular interaction factors are barely predicted precisely. The results often do not match with the experimental binding affinities. Hence, further study is

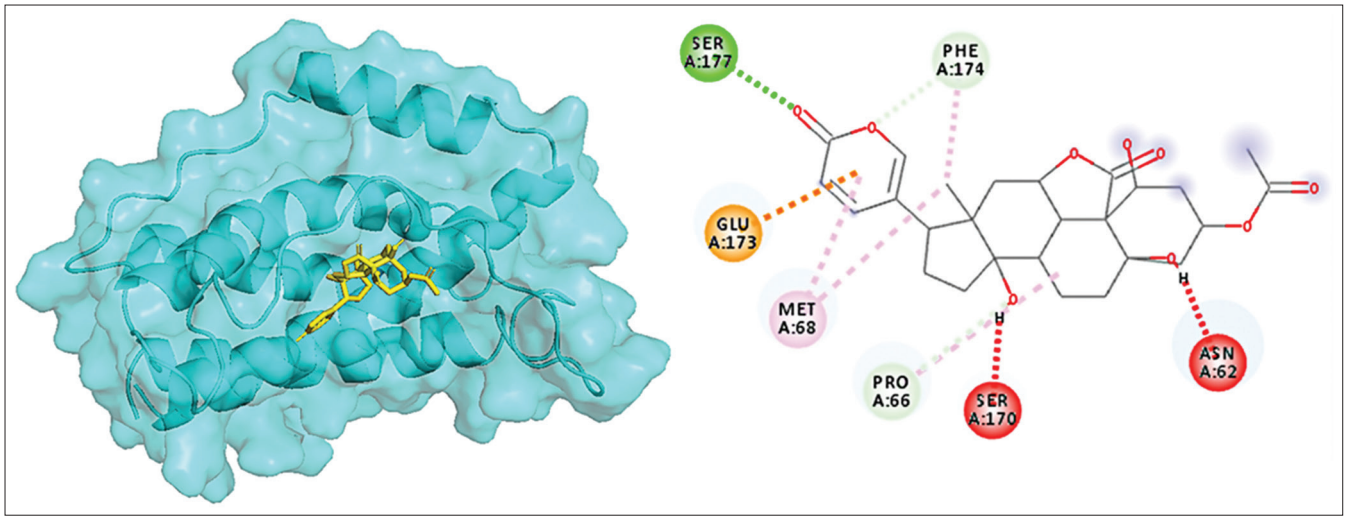

Figure 3: Interaction between Bryophyllin B and IL-6. Bryophyllin B (Yellow), IL-6 (Cyan). Hydrogen Bond (Green Interaction), Hydrophobic Bond (Orange and Pink Interaction), Unfavorable interaction (Red Interaction)

needed to establish the efficacy of these two medicines in treating cytokine storm.

Conclusion

B. pinnatum active compounds, particularly Bryotoxin A and Bryophyllum B, have the promising potential as COVID-19 inhibitors and altering immune response to inhibit cytokine storms. However, further *in vitro* and *in vivo* studies are required.

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