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MECHANISM OF *Phyllanthus niruri* AS IMUNOMODULATOR TO CONTROL COVID 19 INFLAMMATION USING IN SILICO STUDY

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Abstract

Introduction. The cytokine storm in Covid 19 infection is caused by an increase in the activity of several inflammatory mediators and a decrease in anti-inflammatory mediators. Previous research has proven that *Phyllanthus niruri* leaves have an anti-inflammatory effect in experimental animals. This study aims to predict the mechanism of the active compound in *Phyllanthus niruri* leaves as an immunomodulator to suppress the inflammatory process in cases of Covid 19 infection. **Method.** Computational research, using a molecular docking approach. *Phyllanthus niruri* leaf active compounds obtained from Dr. Duke application. The target proteins used were IL-2, IL-6, IL-12 and IFN. The control drug used is Dexamethasone. Visualization of docking results using Drug Discovery Studio. The docking validation indicator uses the value of free energy, Ki, the area of interface interaction and the similarity of the bond position with the amino acid residue of the target protein. The analysis used descriptive analytic compared to control. **Results.** *Phyllanthus niruri* leaf active compounds namely Phylochrysine inhibited IL-2 with a potency of 27%, Rutin and Quercitrin inhibited IL-6 with a potency of 100%, Quercetrin and Lupeol inhibited IL-12 with a potency of 80 and 100%, Quercitrin and lupeol inhibited IFN-γ with a potency of 66% and 55% compared to control. **Conclusion.** *Phyllanthus niruri*leaf active compounds inhibit IL-6 and IL-12 better than inhibition of IL-2 and IFN

Keywords: *Phyllanthus niruri leaves, anti-inflammatory, in silico, covid 19*

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INTRODUCTION

SAR-CoV-2 is the virus that causes Covid 19 disease, which has infected more than 200 million and caused the death of more than 4 million people in the world (1). The cause of death of Covid 19 patients is mostly due to acute respiratory system failure and cytokine storms due to the hyperinflammatory process (2).

Normally when the body is infected with a virus, the immune system will work to eliminate the virus and activate the inflammatory process. The inflammatory process is a biological response of the immune system in response to antigens, cell damage, and toxic materials. The inflammatory process involves the NF-κB, MAPK, and JAK-STAT pathways that cause an increase in the synthesis of inflammatory mediators (3).

Cytokines are the main inflammatory mediators that play an important role in the inflammatory process. Cytokines are produced by immune cells such as macrophages, dendritic cells, natural killer cells, B cells, and T lymphocytes (2). When there is an innate immune response to the virus, the pattern recognition receptors (PRRs) of the virus will be recognized by pathogen-associated molecular patterns (PAMPs) from immune cells. The next process will activate the NF-κB, MAPK, and JAK-STAT pathways thereby increasing the expression of genes encoding pro-inflammatory proteins and increasing the synthesis of pro-inflammatory proteins. The inflammatory process aims to eliminate antigens, clean damaged tissue, and accelerate the healing process. However, excessive inflammation will cause tissue damage and the inflammatory process continues to become chronic inflammation (1,3).

Inflammatory mediators that are widely synthesized and circulate in the blood when infected with SARS-CoV-2 include interleukin-1β (IL-1β), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), (IL)-2, IL-7, IL-10, tumor necrosis factor (TNF), granulocyte colony-stimulating factor (G-CSF), monocyte chemoattractant protein-1 (MCP1; also known as CCL2), macrophage inflammatory protein 1 alpha (MIP1α; also known as CCL3), CXC-chemokine ligand 10 (CXCL10), C-reactive protein, ferritin, and D-dimers. The increase in these inflammatory mediators increases the risk of cytokine storms that increase the morbidity and mortality of Covid 19 patients (3,4).

During the Covid 19 pandemic, the consumption of herbs has increased in the community. Some of the herbs studied and widely used to prevent Covid 19 is *Azadirachta indica A. Juss, Ziziphus lotus* (L.) *Lam, Eucalyptus globulus Labill, Echinacea, Cinchona, Curcuma longa, Curcuma xanthorrhiza*, honey, black seeds, lemon, and ginger. These herbs have the effect of alleviating the complaints of Covid 19 patients and as an anti-inflammatory (5,6,7).

Phyllanthus niruri contains active compounds of polyphenols, flavonoids, terpenes, alkaloids, and saponins. *Phyllanthus niruri* is one of the herbs known to have anti-inflammatory and immunosuppressive effects by reducing the phagocytic activity of macrophages, neutrophil cells, and NK cells, inhibiting the proliferation of B lymphocytes and T lymphocytes, downregulation of Th1 (IL-2 and IFN-γ). and Th2 (IL-4, CD4+, and CD8) (8). However, research related to the potential of *Phyllanthus niruri* leaves as an anti-inflammatory in Covid 19 patients has never been done.

This study aims to predict the mechanism of active compounds in *Phyllanthus niruri* leaves as an anti-inflammatory, especially inhibiting mediators that play a role in the cytokine storm process in Covid 19, namely IL-2, IL-6, IL-12, and IFNγ, in silico. The in silico method is a method that has been widely used to predict the mechanism of action of an active compound in the search for new drugs. This method is done computationally. The first stage is to predict the physicochemical, pharmacokinetic, and toxicity of the active compounds of *Phyllanthus niruri* leaves. The next stage is the docking process using a specific molecular docking approach. The working principle of molecular docking is to measure the affinity of the active compound in this case is considered a ligand to a target protein/receptor. The binding affinity between the ligand and the receptor was validated based on the binding free energy, Ki value, surface interaction, and binding to the active site of the target protein.

METHOD

The type of research used is research with a computational approach to measure the affinity of the active compound of Phyllanthus niruri to IL-2, IL-6, IL-12, and IFNγ protein. The active compound from *Phyllanthus niruri* leaf was obtained from Dr, Duke on line which consisted of *Phyllanthus niruri*. The 3-dimensional structure of the active compound in *Phyllanthus niruri* leaf and target protein was obtained from Pubchem and Uniprot. The control drug used was dexamethasone which is an immunosuppressive drug. Prediction of physicochemical properties and ADMET using online PKCSM

(http://biosig.unimelb.edu.au/pkcsm/prediction). The naming of the SMILES canonical active compound was copied and pasted in the PKCSM application, then an ADMET search was carried out to obtain the results of the physicochemical properties, ADME, and toxicity of the active compound. The indicators of the physicochemical properties of the active compounds used in neem leaves are chemical structure, molecular weight, log P, hydrogen acceptor, and hydrogen donor. The pharmacokinetic indicators used were absorption assessed from the value of absorption in the intestine, distribution was assessed from the ability to penetrate the blood-brain barrier and unbound compounds, metabolism was assessed from the ability to affect P450 enzyme activity in the liver, and excretion was assessed from the clearance carried out by the kidneys, liver, and kidneys. intestines. Toxicity is assessed from the presence of hepatotoxic effects and the potential to cause carcinogenic effects (9,10).

Docking process using software dockingserver.com. the docking stage begins with the preparation of ligands and proteins. The 3-dimensional structure of the active compound and protein is stored in the PDB file. Next, docking between the control and the target protein was carried out to determine the grid box. The docking process was repeated 10 times. The active site validation process was determined based on the bond between the control drug and the target protein which had the smallest free energy value and an RMSD of less than 2Å. The indicators used to measure the strength of the binding affinity of the active compound with the target protein were the value of binding free energy, inhibition constant, surface interaction area, and binding to the active site of the target protein compared to the control. The smaller the value of pure energy, the smaller the value of the inhibition constant, the larger the surface interaction area, and the more amino acid residues on the active site of the protein.

The same binding target as the control, then the affinity of the active compound for the target protein was considered strong. Data analysis used descriptive analytic compared to control (11,12).

RESULTS

5th Rules Of Lipinski And Pharmacokinetic Of Active Compounds Of *Phyllanthus niruri* Leaf

Prediction of the solubility of active compounds in *Phyllanthus niruri* leaves using the PKCSM tool on line. The indicators of physicochemical properties used are molecular weight, logP, hydrogen acceptor, hydrogen donor, and 5th rules of Lipinski. The results of the physicochemical active compounds of *Phyllanthus niruri* leaves can be seen in **table 1** (13).

Table 1. Physicochemical Active Compounds of *Phyllanthus niruri* Leaves

No	Nama Senyawa Aktif	CID	BM	Log P	HBA	HBD	5th rules of Lipinski
1	Phyllochrysine	267769	217.268	1.405	3	0	Yes
2	Phyltetralin	11223782	416.514	3.9342	6	0	Yes
3	Lupeol	259846	426.729	8.0248	1	1	Yes
4	astragalin	5282102	448.38	-0.2445	11	7	Yes
5	Brevifolin-Carboxylic-Acid	139206794	687.709	6.0724	12	4	No
6	3,5,7-Trihydroxyflavone	5281616	270.24	2.5768	5	3	Yes
7	Quercetin	5280343	302.238	1.988	7	5	Yes
8	4- methoxynorsecurinine	101091319	233.26	2.25	4	0	Yes
9	Ene-3-Beta-Ol-Acetate	13723179	356.54	3.98	2	0	Yes
10	Linteralin	353260	394.50	3.19	4	3	Yes
11	Niranthin	13989915	432.51	4.32	7	0	Yes
12	Phyllohrysine	267769	217.26	2.37	3	0	Yes
13	Quercitrin	5280459	448.38	1.27	11	7	No
14	Rutin	5280805	610.52	2.43	16	10	No
15	Phyllantin	358901	418.52	4.26	6	0	Yes

The 5th rule of Lipinski is used to determine the possibility of an active compound having the ability like a drug when given orally. Lipisnki's rule can also predict the solubility of an active compound. The higher the solubility of a compound, the greater the bioavailability of the compound. An active compound is said to have high solubility if the molecular weight is less than 500Da, the log P is less than 5, the hydrogen donor is less than 10, and the acceptor hydrogen is less than 5.

Based on the results of physicochemical predictions, it was found that the active compounds phyllochrysine, phyltetralin, lupeol, astragalin, 3,5,7-trihydroxyflavone, quercetin, 4-methoxynorsecurinine, ene-3-beta-ol-acetate, linteralin, niranthin, phyllohrysine, and phyllohrysine. soluble in water, while brevifolin-carboxylic-acid, quercitrin and rutin are insoluble in water.

To see the bioavailability and safety of the active compounds in Phyllanthus niruri leaves, the PKCSM online tool was used. The absorption indicator uses the absorption value in the intestine, the distribution uses the unbound fraction value and the ability to penetrate the BBB, metabolism uses the ability as a substrate or CYP450 inhibitor, excretion uses the clearance value, and toxicity uses carcinogenic and hepatotoxic predictions can be seen in **table 2** (13,10).

Table 2. Prediction of Pharmacokinetics and Toxicity of Active Compounds of *Phyllanthus niruri* Leaves

Active compounds	Absorbtion		Distribution		Metabolism							Excretion	Toxicity	
	Human intestinal Absorption (%)	Permeability (log mol/L)	Fraction unbound (Fu)	BBB (log BB)	CYP 2D6 substrat	CYP 3A4 substrat	CYP 1A2 inhibitor	CYP 2C19 inhibitor	CYP 2C9 inhibitor	CYP 2D6 inhibitor	CYP 3A4 inhibitor	Clearance (log ml/min/kg)	Hepato toxic	AMES
Phyllochrysine	96.859	-2.036	0.669	0.006	No	No	No	No	No	No	No	1.074	Yes	No
Phyltetralin	100	-5.881	0	-1.517	No	Yes	No	Yes	Yes	No	Yes	0.455	No	No
Lupeol	95.782	-5.861	0	0.726	No	Yes	No	No	No	No	No	0.153	No	No
astragalin	48.052	-2.863	0.218	-1.514	No	No	No	No	No	No	No	0.2462	No	No
Brevifolin-Carboxylic-Acid	77.387	-2.892	0.248	-2.554	No	No	No	No	No	No	No	0.489	No	No
3,5,7-Trihydroxyflavone	93.985	-3.335	0.142	-0.748	No	No	Yes	Yes	Yes	No	No	0.256	No	No
Quercetin	77.207	-2.925	0.206	-1.098	No	No	Yes	No	No	No	No	0.407	No	No
4- methoxynorsecurinine	97.121	-1789	0.699	-0.1	No	No	No	No	No	No	No	1.135	No	No
Ene-3-Beta-Ol-Acetate	97.051	-6.445	0	0.635	No	Yes	No	No	No	No	No	0.59	iya	No
Linteralin	91.642	-3.876	0.011	-0.829	No	Yes	No	Yes	Yes	No	No	0.701	No	No
Niranthin	98.521	-5.562	0	-1.644	No	Yes	No	Yes	Yes	No	Yes	0.426	No	No
Phyllohrysine	96.859	-2.036	0.669	0.006	No	No	No	No	No	No	No	1.074	Yes	No
Quercitrin	52.709	-2903	0.13	-1.495	No	No	No	No	No	No	No	0.364	No	No
Rutin	23.446	-2.892	0.187	-1.899	No	No	No	No	No	No	No	-0.369	No	No
Phyllantin	98.349	-5.712	0	-1.348	No	Yes	No	Yes	Yes	No	Yes	0.591	No	No

The pharmacokinetic prediction results showed that phyllochrysine, astragalin, brevifolin-carboxylic-acid, quercetin, 4-methoxynorsecurinine, and phyllohrysine, were well absorbed in the intestine, had high solubility, mostly distributed in the free form, were not toxic to neuronal cells, were not toxic to neurons. activates or inhibits the CYPP 450 enzyme, excreted through the kidneys, liver, and gastrointestinal tract, is non-toxic and has no potential as carcinogenic.

Molecular Doking of Active Compound of *Phyllanthus niruri* Leaf to IL-2,IL-6, IL-12 and IFNγ Protein

The results of docking between the active compounds of *Phyllanthus niruri* leaves and the target proteins used, namely IL-2, IL-6, IL-12, and IFN can be seen in **tables 3,4,5, and 6.**

Table 3. Molecular Docking of *Phyllanthus niruri* Leaf Active Compounds Against IL-2. Protein

No	Active Compound	ID	Free Energy Binding (Kcal/mol)	Konstant Inhibition (μM)	Surface Interaction (Å)	Intermolecular Interaction	Bonding to active Site of IL-2 Protein (%)
1	Dexamethasone	5743	-5.95	3.82	810.251	Hydrogen bond: Lys15 Hydrofobic bond: Trp62, Tyr155, Trp230, Phe156 Polar bond: Asp14, Asp41, Asn150, Glu111 Halogen bond: Lys15 Others : Glu153, Glu44	100
2	Rutin	5280805	-10.32	27.05 uM	663.518	Hydrofobic bond: Leu 379, Leu 377 Polar: Lys 376, Gln 378 Others: Gln 380	0
3	Quercitrin	5280459	-8.53	555.31 uM	565.326	Hydrofobic bond: Leu 379 Polar bond: Gln 380, Glu 381, Arg 305 Others: Leu 377	0
4	Astragalin	5282102	-6.73	11.76	619.454	Hydrofobic bond: Leu 379 Polar bond : Gln 380, Arg 305. Arg 331, Lys 376 Others : Leu 377	0
5	Ene-3-Beta-Ol-Acetate	13723179	-6.39	20.54 uM	635.190	Hydrofobic bond : Trp30, Leu 379 Polar bond : Glu 378 Others: Arg 305, Glu 381	0
6	Quercetin	5280343	-5.74	62.28	492.968	Hydrofobic bond: Leu 379 Polar bond : Glu 381, Arg 305 Others: Gln 380, Leu 377	0
7	Phyllochrysine	267769	-5.32	3.55	530.817	Hydrofobic bond: Trp340, Tyr155 Polar bond : Trp62, Glu153 Others :Arg66, Pro154, Asp65	27
8	Phyltetralin	11223782	-4.94	8.00	975.322	Hydrofobic bond: Trp62, Tyr155, Trp340, Phe156, Pro154, Tyr210 Polar bond : Glu153, Asn12, Arg66 Others : Lys42, Glu44, Asp14, Lys15, Asp65	64

Table 4. Molecular Docking of *Phyllanthus niruri* Leaf Active Compounds Against IL-6 . protein

No	Active compound	ID	Free Energy Binding (Kcal/mol)	Konstant Inhibition (µM)	Surface Interaction (Å)	Intermolecular Interaction	Bonding to Active site of IL- 6 protein
1	Dexametahone	5743	-7.84	1.81	694.028	Polar bond: Glu129, Arg154, Thr130 Hydrofobic bond: Pro157, Phe136 Others: Thr134, Glu133	100
2	Rutin	5280805	-9.44	120.96	765.178	Hydrogen Bond: Thr 130, Thr134 Polar bond : Arg 154, Glu129 Cation-pi: Phe136 Hydrofobic bond: Pro157 Others : Thr158, Glu133	100
3	Quercitrin	5280459	-7.76	2.06	620.223	Polar bond : Thr134, Thr130 Hydrofobic bond: Pro157, Phe136 Others : Thr 158, Asp155	100
4	Lupeol	259846	-7.41	3.70	674.124	Hydrofobic bond: Phe136, Pro158 Others : Thr158, Thr130, Thr134	43
7	Phyllohrysine	267769	-6.78	10.80	495.714	Hydrogen Bond: Thr134 Polar bond: Asn135 Cation-pi: Phe136 Hydrofobic bond Pro157 Others : Arg154, Glu133, Lys151	71
5	Astragalin	5282102	-6.51	8.11	754.751	Hydrogen Bond: Phe136 Polar bond : Arg154 Hydrofobic bond: Pro157, Ala152 Others Thr130, Glu133, Thr134	86

Table 5. Molecular Docking of *Phyllanthus niruri* Leaf Active Compounds Against IL-12 . protein

No	Active compound	ID	Free Energy Binding (Kcal/mol)	Konstant Inhibition (µM)	Surface Interaction (Å)	Intermolecular Interaction	Bonding to Active site of IL-12 protein
1	Dexamethasone	5743	-5.95	43.43	534.756	Hydrofobic bond: Ala 40 Polar bond: Arg 38 Others: Lys43, Glu46, Ala 92	100
2	Quercitrin	5280459	-8.53	0.55	566.326	Hydrofobic bond: Lys43 Polar bond: Glu46, Arg 38 Others: Ala40	80
3	Rutin	5280805	-7.88	1.67 uM	-5249.492	Polar: Arg 153, Thr 134, Gln 39	0
4	Lupeol	259846	-7.31	4.35	617.557	Ikatan hidrogen: - Kation-pi: - Hidrofobik: Ala 40 Polar: Arg38 lain lain :Glu46, Lys43, Ala 92	100
5	Ene-3-beta-ol-acetate	13723179	-6.39	20.54	635.199	Hydrofobic bond: Trp47, Phe 103, Leu 45, Ala 61 Polar bond: - lain lain : Glu46, Asp62	20
6	Astragalin	5282102	-6.73	11.76	619.454	Hydrofobic bond: Ala 61 Polar bond : Glu 46 Others : Trp47, Phe 103	0
7	5,3',4'-Trihydroxyflavonone -7-O-Alpha-L-(-)-Rhamnopyranoside	71514077	-5.48	96.49	461.953	Hydrofobic bond: Ala 40 Others: Lys43, Glu 46 , Arg 38	80
8	Quercetin	5280343	-5.74	62.28	492.968	Hydrofobic bond: Ala 40 Polar bond : Lys 43, Arg 38 Others: Glu46	80

Table 6. Molecular Docking of *Phyllanthus niruri* Leaf Active Compounds Against IFN-γ protein

No	Active compound	ID	Free Energy Binding (Kcal/mol)	Konstant Inhibition (μM)	Surface Interaction (Å)	Intermolecular Interaction	Bonding to Active site of IFN γ protein
4	Dexamethasone	5743	-6.67	12.86	585.058	Hydrofobic bond : Phe70, Leu69, Val74, Leu138, Phe55, His142, Leu141 Polar bond: - Others : Pro56, Thr77	100%
1	Quercitrin	5280459	-7.62	2.60	604.622	Hydrogen bond: Thr77 Hydrofobic bond : Phe70, Val74 Polar bond: His142 Others : Leu69, Leu138, Thr66	66
2	Lupeol	259846	-7.22	5.07	674.232	Hydrofobic bond : Phe70, Phe55, Leu69, Leu138 Polar bond: - Others :Thr77	55
3	Ene-3-beta-ol-acetate	13723179	-6.86	9.37	601.976	Hydrofobic bond : Phe70, Val74, Phe55, Leu138, Leu141, Val54, Leu69 Polar bond : - Others : Thr77	77
5	Astragalin	5282102	-6.57	15.16	651.641	Hydrofobic bond Phe70, Leu69, Leu138 Polar bond : His142, Thr77 Others : Thr66	55
6	5,3',4'-Trihydroxyflavonone-7-O-Alpha-L-(-)-Rhamnopyranoside	71514077	-6.36	21.78	520.584	Hydrogen bond: Tyr78 Hydrofobic bond Phe55, Val54, Pro53, Met71 Polar bond: - Iain Iain : Lys57	11
7	Quercetin	5280343	-5.89	48.09	494.85	Hydrogen bond: His142, Thr77 Cation-pi: Phe70 Hydrofobic bond Leu138 Polar bond: - Others : Leu69, Thr66	55

Note: Of the 15 active compounds found in *Phyllanthus niruri* leaves, only the active compounds that have good affinity are shown in the table.

Determination of the affinity of the ligand to the receptor in this study used indicators of the value of free bond energy, Ki, interaction surface area, and intermolecular interactions. The free bond energy is the amount of energy required when the ligand binds to the receptor to form a stable complex bond. The smaller the value of free energy, the more stable the bond. The value of the inhibition constant indicates the affinity of the ligand to the receptor. The smaller the value of Ki indicates the greater the affinity and the smaller the dose of the ligand needed to cause an inhibitory effect on receptor activity. The surface area shows how large the area formed due to the bond between the ligand and the receptor. Intermolecular interactions show the bond between the ligand molecule and the amino acid residues that make up the active site of the receptor.

The docking results showed that dexemethasone has a good affinity for IL-2, IL-6, IL-12, and IFN proteins with binding free energies of -5.95 kcal/mol, - 7.84 kcal/mol, - respectively. 95 kcal/mol and – 6.57 kcal/mol. The Ki value is 3.83μM. 1.8 M, 43.48 M, and 12.86 M. The docking process uses specific docking so that the determination of the active site of each target protein is based on the results of the docking between dexamethasone and the target protein.

Cytokine storms are one of the causes of death in Covid 19 patients. This condition is one of the complications of SARS-Cov-2 infection, which mainly occurs in patients who have co-morbidities such as diabetes mellitus and old age. The presence of hypersensitivity, when infected with the SARS-CoV-2 virus, causes macrophage cells, dendritic cells, epithelial cells, endothelial cells, neutrophils, T lymphocytes, and naive B lymphocytes to produce

inflammatory mediators in excess. This condition is known as a cytokine storm. Several inflammatory mediators that are known to increase during a cytokine storm are IL-1, TNFα, IL-6, IL-12, and INF. Excessive increase in inflammatory mediators in the blood will damage blood vessel capillaries, laveolar cells, and multi-organ function disorders occur which can lead to death (3,4,14).

Dexamethasone is known to have an immunosuppressant effect. The mechanism of action of dexamethasone as an immunosuppressant is through the mechanism of inhibiting the proliferation and differentiation of naive T cell lymphocytes (15), inhibiting IL-6 (16), causing downregulation of B lymphocytes and signaling tools. Like Receptor 7 signaling, upregulates anti-inflammatory cytokine IL-10, inhibits antigen presentation, inhibits expression of co-stimulatory molecules and cytokine production (IL-1, TNF, and IL-6), chemokines, and other soluble mediators (such as prostaglandin E2, leukotrienes, and histamine). Dexamethasone also inhibits the expression of NfKB genes that play a role in cytokine synthesis (17). The results showed that the administration of dexamethasone to patients with Covid infection in combination with Remdesivir was able to accelerate the healing process and reduce the mortality of Covid 19 patients (18).

Based on the criteria for determining the affinity of the active compound to the target protein, it can be seen that the active compound in *Phyllanthus niruri* leaves phyllohrysine can inhibit IL-2 although it is weaker than dexamethasone. Phyllohyrisine binds to 27% of the active site of the IL-2 protein. Several active compounds such as rutin, quercitrin, astraglin, and ene-3-beta-ol-acetate had lower free energy than control, but did not bind to the active site of the IL-2 protein. Researchers suspect that the three active compounds have different effects on IL-2 or are non-competitive inhibitors with dexamethasone to inhibit IL-2.

Rutin and quercitrin have a high affinity for IL-6 protein approaching the control of dexamethasone 6. Rutin and quercitrin have free binding energies of -9.44 kcal/mol and -7.76 kcal/mol lower than dexamethasone, and bind 100% of the active site of IL. -6 is the same as dexamethasone. Luteol, phyllohrysine, and astragalin have lower affinity because they have higher free binding energy than dexamethasone to inhibit IL-6, and lower active site amino acid binding than dexamethasone.

Lupeol and quercitrin have a higher affinity for IL-12 protein than 3,5,7-trihydroxyflavone, quercetin, and ene-3-beta-ol-acetate. Lupeol and quercitrin have free energies of -7.31 kcal/mol and -8.53 kcal/mol which are lower than dexamethasone, and bind 100% and 80% compared to dexamethasone, respectively. Rutin although has the smallest free

binding energy compared to other active compounds, but does not bind to the active site of the target protein. Thus, rutin is thought to have other effects or act as a non-competitive inhibitor with dexamethasone to inhibit IL-12.

Quercitrin, lupeol, ene-3-beta-ol-acetate, and astragalin are active compounds that have good affinity for IFNγ but are lower than control. Quercitrin, lupeol, ene-3-beta-ol-acetate, and astragalin have free bond energies of -7.62 kcal/mol, -7.22 kcal/mol, -6.86 kcal/mol and -6.457 kcal/mol, respectively by binding to the active site of IFN. of 66%, 55%, 77%, and 55%.

Based on the physicochemical properties, rutin and quercitrin are compounds that do not meet the 5th rules of Lipinski, while Lupeol meets the 5th Rules of Lipinski. Active compounds that meet Lipinski's criteria have high solubility values. High solubility will affect the absorption process, so that levels in the blood also increase (10). ADMET of these three compounds has good absorption except rutin and quercitrin, does not penetrate the blood-brain barrier, in the blood in free form, does not activate or inhibit CYP450 enzymes, is excreted through the kidneys, liver and gastrointestinal tract, and is not toxic or carcinogenic.

The molecular prediction results of routine docking have the potential to inhibit IL-6, while quercitrin and lupeol have the potential to inhibit IL-6 and IL-12, so that future research needs to be done to increase the solubility of rutin and quercitrin. In the future, it is necessary to conduct in vivo studies to compare the anti-inflammatory effects of *Phyllanthus niruri* leaves using crude extracts or single compounds, as well as toxicity tests to determine safety.

CONCLUSION

Phyllanthus niruri leaf active compounds, namely Rutin, Quersitrin, and Lupeol, have potential as an anti-inflammatory in Covid 19 cases through the mechanism of inhibition of IL-6 and IL-12.

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CONFLICT OF INTEREST

The author states that there is no conflict of interest in this study.

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