

# Identification of Potential Ebola Virus Nucleoprotein (EBOV NP) Inhibitor Derivate from Various Traditional Medicinal Plants in Indonesia: *in silico study*

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**ABSTRACT:** Ebola virus disease is caused by Ebolavirus infection. Within infection, Ebola nucleoprotein (EBOV NP) is essential part for virus proliferation. Recent report showed that the outbreak was happened in Congo on February 2021. Although million cases were reported, the drug is remain unavailable. However, Indonesia had a high diversity of plants as traditional drugs. This research aimed to identify the traditional drug plants as potential inhibitor for EBOV NP. The SMILE notation of 65 identified compounds were collected from PubChem and 3D structured of EBOV NP (PDB ID: 4Z9P) was obtained from PDB. Molecular docking was conducted between selected compounds and EBOV NP. Clabistrin C was selected as a control. Complex of compounds-EBOV NP and its amino acid residues were depicted by using Chimera X and LigPlot. Several potential compounds were selected for pharmacological activity prediction by PASS Online, toxicity analysis by ProTox-II, and drug likeness analysis with SWISSADME. Result showed that among the docked compound, hesperidin, cucurbitacin, ginsenoside RH2, and ginsenoside RO had lower binding energy compared to control. Moreover, all of those compounds had comparable hydrogen and hydrophobic interactions with EBOV NP. Further analysis showed it has potential biological function for Ebola disease, such as antiviral, antioxidant, and immunostimulant. All those compounds had low toxicity. As conclusion, there are four promising compounds that potentially inhibited the Ebolavirus proliferation.

**Keywords:** antiviral drug; secondary metabolites; viral infection; virtual screening

## 1. Introduction

Ebola viruses are negative stranded RNA viruses that belong to the Filoviridae family and it is endemic to regions of west and equatorial Africa. It known by primarily transmitted by human-to-human contact with infected body fluids and corpses [1]. Ebolaviruses were first identified in 1976, over 41 outbreaks of Ebola disease have been identified in sub-Saharan Africa, mostly in Sudan, Uganda, Democratic Republic of Congo, and Gabon. Until 2020, there was 34,644 cases and 14,987 deaths around the world. In the latest outbreak in the 14 February 2021 at guinea, the cases showed symptoms of diarrhea, vomiting and bleeding. Other cases showed that among the 7 other cases, five have died (4 probable and 1 confirmed with ebola virus) and the others were still in the isolation at dedicated health care facilities [2].

Ebola Nucleocapsid RNA is complexed with the NP, VP35, VP30, and L proteins [3]. The infection mechanism of Ebola virus was started by targeting the immune cells like endothelial cells, liver cells, and several types of immune cells. When the virus keep growing were lead to injury to the blood vessels, it could induce the blood clot and liver damage [4]. Ebola virus nucleoprotein (EBOV NP) were one of the protein that responsible in viral transcription and replication by direct interaction with EBOV RNA, VP35, and transcription regulator VP30 [5]. In particular, recent results have clearly demonstrated that viral NP could be directly used as the target for antiviral development [6] and raising a great potential to find new antiviral agents. Various secondary metabolites derived from traditional medicinal plants is considered for having huge potential to be developed as antiviral drug. Therefore, this research aimed to investigate the secondary metabolites from Indonesian traditional medicinal drug which had potential ability to be developed as antiviral drug for Ebola disease.

## 2. Materials and method

### 2.1. Sample preparation

Sixty five active compounds data of traditional drugs plants in Indonesia were obtained from PubChem database (<https://pubchem.ncbi.nlm.nih.gov/>). Calbistrin C was selected as referenced compound. In brief, previous research showed that it had low binding affinity about -7.9228 kcal/mol and RMSD value 2.3913 [7]. Furthermore, the ID number of each compound and notation of canonical simplified molecular-input line-entry system (SMILES) was collected for further analysis. Furthermore, the 3D structure of each compound was collected in sdf format. The process of minimization was conducted by using the Open Babel plug-in within PyRx software. It was essential for preparing compound as ligand for molecular docking analysis. The 3D structure of Ebola virus nucleoprotein (EBOV NP) protein was obtained from the Protein Data Bank (PDB) database (<https://www.rcsb.org/>) with PDB ID 4Z9P. The unnecessary molecules including water was removed from EBOV NP structure by using Chimera. Furthermore, protein structure was added by hydrogen as preparation for further analysis.

### 2.2. Molecular docking simulation and visualization of complex ligands-EBOV NP

The interaction prediction between EBOV NP and 65 ligands were conducted by using molecular docking analysis. The process performed by using Autodock Vina on the Pyrx software. Docking process was addressed to the specific site of EBOV NP. Furthermore, the binding affinity score was collected and compared to get the potential candidate of drug compound. The complexes of EBOV NP and potential ligands were visualized by using Chimera software and analyzed by using LigPlot software to identify the amino acid residues interaction.

### 2.3. Pharmacokinetic prediction of potential ligands

Four potential compounds as result of molecular docking were listed and analysed based on the Lipinski rule of 5. The canonical SMILE of each potential compounds was analysed by using

SWISS ADME (<http://www.swissadme.ch/>) [8]. Furthermore, the analysis result of each component Lipinski rule of 5 were collected.

#### **2.4. Pharmacological activity prediction of potential ligands**

The pharmacological activity of selected potential compounds were identified by using PASS Online webserver (<http://way2drug.com/pass-online/>). Various pharmaceutical activity was analyzed based on score of probability of activity (Pa) and probability of inactivity (Pi). The Pa score was varied from 0-1 which suggested the level activity of compounds [9,10].

#### **2.5. Toxicity prediction of potential ligands**

Selected potential compounds were addressed for toxicity prediction. Analysis was performed by using ProTox-II ([https://tox-new.charite.de/protox\\_II/](https://tox-new.charite.de/protox_II/)) by submitting the canonical SMILE of each compound [11]. Result of analysis was determined the compounds into six class of toxicity.

### **3. Result and discussion**

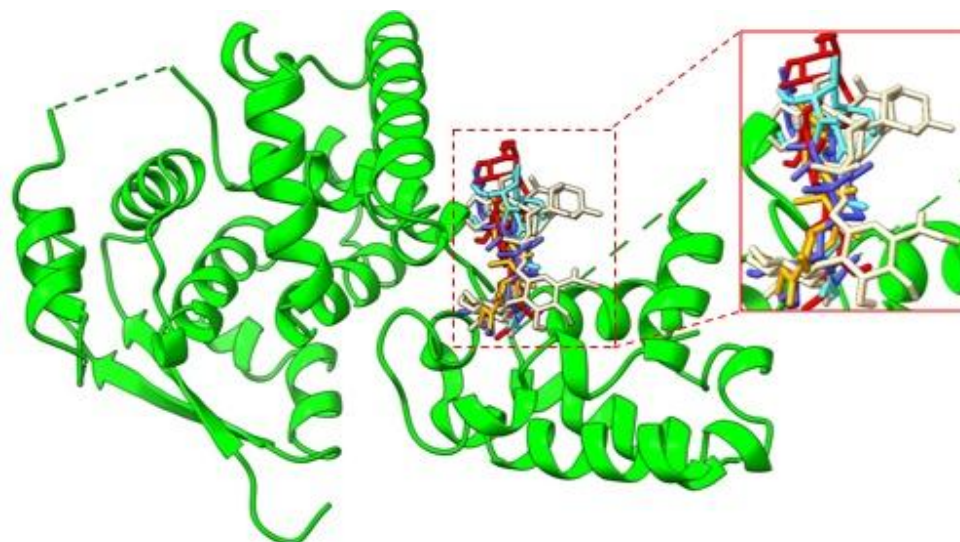
Sixty-five ligands in this study are obtained from various traditional plants in Indonesia which believed had an antiviral function by ancestors. As tropical country, Indonesia is considered as mega-diversity country in fauna and flora diversity. Various plants were found in Indonesia so that it considered by having huge potential to be developed for pharmaceutical function [12]. Therefore, there are many Indonesian people that utilizing plants as medicine so that it known as traditional drug plants. It believed safe and culturally acceptable. In brief, all those ligands samples could be isolated range from cucurbitaceous plants, ginseng, tea, pepper, pomegranate [13-17].

Ebola virus nucleoprotein (EBOV NP) is protein which had essential function for virus replication. It consists of 739 amino acid residues and it has structure which could be divided into

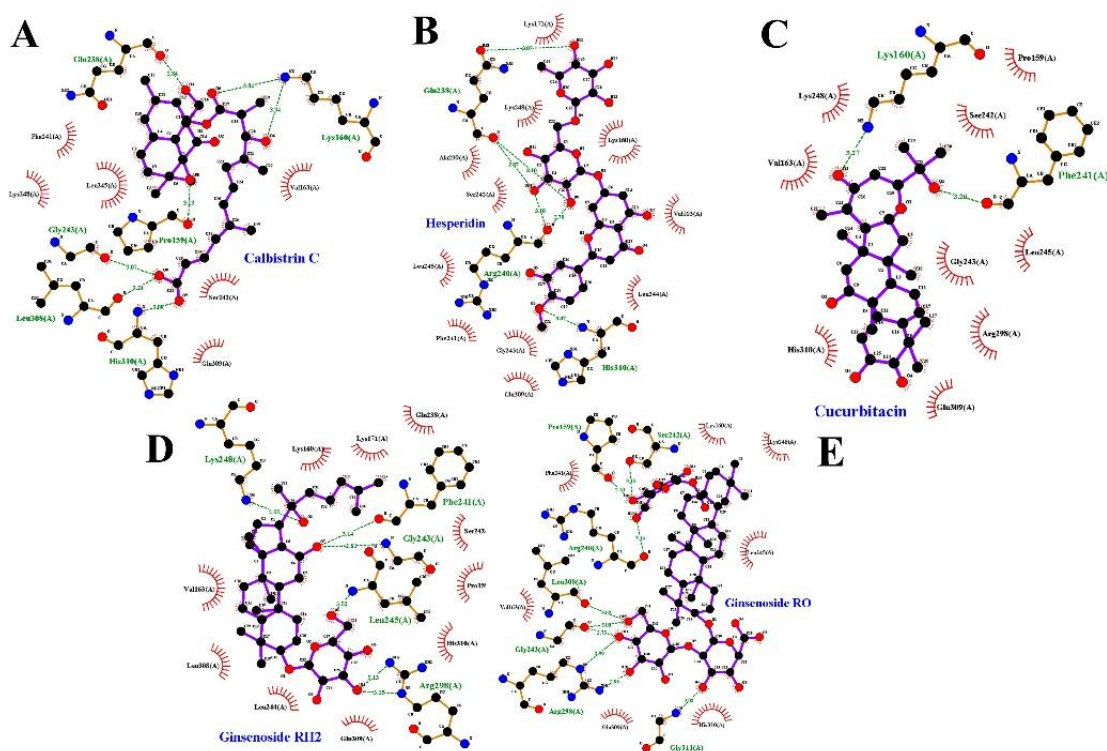
N-tail, N-lobe, C-lobe, and C tail. Moreover, it could mediate the process during virion transcription process and protect the RNA genome from de-gradation. EBOV NP is also known for contributing into budding and assembly process within viral life cycle. Therefore, it become an attractive target for drug development [18]. Study of interaction of protein EBOV NP-ligand was demonstrated by using molecular docking analysis. The docking process was addressing all ligands to bind into specific site with coordinate center X: 6.9108, Y: 11.1981, Z: 3.5358; and dimensions (angstrom) X: 19.1764, Y: 23.8639, Z: 24.8673 (Figure 1). This process was aimed to predict the ability of the ligands extracted from various traditional medicinal plants to bind and inhibit the activity of EBOV NP. The ability of ligand to bind into protein was demonstrated by the binding affinity score. Negative score is defined as strong interaction between ligands and protein.

The utilization of various traditional drug compounds as inhibitor candidate of EBOV NP showed that 17 active compounds had lower binding energy as compared to control, then top four compounds with the lowest binding energy were taken for visualization and further analysis (Table 1). In brief, hesperidin, cucurbitacin, Ginsenoside RH2 and Ginsenoside RO had binding affinity score about -7,6 kcal/mol, -7,6 kcal/mol, -7,5 kcal/mol, and -7,4 kcal/mol, respectively. Those four ligands showed lower binding affinity as compared to the Calbistrin C with score -6,4 kcal/mol. Calbistrin C (ZINC4262121) was demonstrated as the best ligand from previous analysis that bind to EBOV NP. Therefore, it is chosen as compound reference in this research.

Figure 1 showed that all ligands were bound into the same location with the native ligand. Moreover, those ligands also successfully formed hydrogen and hydrophobic bond within the binding pocket of EBOV NP. Complex of EBPV NP-potential ligands was addressed for amino acid residue analysis. Results demonstrated that all those ligands could form hydrogen bond and hydrophobic interactions in the binding pocket of EBOV NP



**Figure 1.** Ligands Hesperidin (red), Cucurbitacin (orange), Ginsenoside RH2 (purple blue), Ginsenoside RO (wheat), and reference compound Calbistrin C (cyan) were bind into specific site of EBOV NP



**Figure 2.** Amino acid residues within EBOV NP with potential ligands, including Calbistrin C (A), Hesperidin (B), cucurbitacin (C), Ginsenoside RH2 (D), and Ginsenoside RO (E)

(Figure 2). Each of potential ligands shared comparable amino acid residues which similar to the Calbistrin C, including Arg240, and Arg298. Hesperidin had hydrogen bonds with Gln238, and His310, while cucurbitacin had hydrogen with Lys160 (Table 2).

Further analysis was conducted by addressing those four potential ligands to the pharmacoki-

netics and toxicity investigation. There are certain criteria of pharmacokinetics and drug likeness of compound so that it could be developed as drug candidate. It defined as Lipinski rule of five which originally proposed by Lipinski. In brief, the Lipinski's rule of five is including criteria such as molecular weight less than 500 g/mol, H-bond donor more than 5, H-bond acceptor less than

**Table 1.** The result of binding affinity score between sixty five potential ligands and EBOV NP

No	PubChem ID	Compound	Binding Energy (kcal/mol)
1	10621	Hesperidin	-7.6
2	119287	Cucurbitacin	-7.6
3	119307	Ginsenoside RH2	-7.5
4	11815492	Ginsenoside RO	-7.4
5	275182	Berberamine	-7.3
6	64945	Ursolic Acid	-7.3
7	65064	Epigallocatechin gallate	-7.3
8	11787114	Silvestrol	-7.2
9	64971	Betulinic Acid	-7.2
10	1794427	Chlorogenic Acid	-6.8
11	6918670	Ingenol Mebutate	-6.8
12	3213	Ellipticine	-6.7
13	5287969	Flavopiridol	-6.7
14	12855889	ginsenoside RC	-6.7
15	3220	Emodin	-6.5
16	969516	Curcumin	-6.5
17	5280343	Quercetin	-6.4
<b>18</b>	<b>6474046</b>	<b>Calbistrin C (reference control)</b>	<b>-6.4</b>
19	5280863	Kaempferol	-6.2
20	9064	Catechin	-6.2
21	5281654	Isorhamnetin	-6.1
22	5281708	Daidzein	-6.1
23	638024	Piperine	-6.1
24	5280961	Genistein	-6.0
25	6928	2,2'-metilen bis[6-(1,1- dimetiletil)-4-etil] fenol	-6.0
26	5351344	Combretastatin	-5.9
27	3885	Beta-Lapachone	-5.8
28	285033	Homoharingtonie	-5.6
29	370	Gallic acid	-5.3
30	91354	Aromadendrene	-5.2
31	5281794	6-shogaol	-5.1
32	72	Protocatechuic	-5.0
33	2519	Caffein	-4.9

No	PubChem ID	Compound	Binding Energy (kcal/mol)
34	6508206	$\alpha$ -humulene	-4.9
35	689043	Caffeic Acid	-4.9
36	111037	alpha-Terpinyl acetate	-4.8
37	4276	Myristicin	-4.8
38	445858	Ferulic acid	-4.8
39	521214	junipper-campor	-4.8
40	10742	Syringic acid	-4.7
41	3026	Dibutil ftalat	-4.7
42	637542	P-Coumaric Acid	-4.7
43	643820	Nerol	-4.7
44	6651	Terpin	-4.7
45	8468	Vanillic acid	-4.7
46	5280450	9,12-Asam Oktadeka Dienoat (lionelic acid)	-4.6
47	5281783	etil p-metoksi sinamat	-4.6
48	17100	Alpha terpineol	-4.5
49	18818	Sabinene	-4.5
50	91749664	2alpha,9-Dihydroxy-1,8-cineole	-4.5
51	11148	Trimiristin	-4.5
52	10819	Perillyl Alcohol	-4.4
53	3314	Eugenol	-4.4
54	36284	4-Ipomeanol	-4.4
55	7460	1-Phellandren	-4.4
56	14896	beta Pinene	-4.3
57	26447	menthone	-4.3
58	590536	2-isopropylbenzaldehyde	-4.3
59	6616	camphene	-4.3
60	7463	p-cimene,	-4.3
61	985	Asam palmitat	-4.3
62	1254	Menthol	-4.2
63	22311	limonene	-4.2
64	8748	beta-terpineol	-4.2
65	11005	Myristic Acid	-4.1

**Table 2.** List of amino acid residues within complex of EBOV NP and potential ligands

Ligands	Hydrogen bonds	Hydrophobic interactions
Hesperidin	<u>Gln238: 3.07, 3.10, &amp; 2.87 Å</u> <u>Arg240: 3.10 &amp; 2.70 Å</u> His310: 3.07 Å	Lys160, <u>Val163</u> , Lys171, Ala239, <u>Phe241, Ser242</u> , Gly243, Leu244, <u>Leu245, Lys248, Glu309</u> .
Cucurbitacin	Lys160: 3.27 Å Phe241: 3.26 Å	Pro159, <u>Val163, Ser242</u> , Gly243, <u>Leu245, Lys248</u> , Arg298, <u>Glu309</u> , His310.
Ginsenoside RH2	Phe241: 3.14 Å; Gly243: 2.81 Å Leu245: 3.02 Å; Lys248: 2.90 Å Arg298: 3.13 & 3.15 Å	Pro159, Lys160, <u>Val163</u> , Lys171, Gln238, Ser242, Leu244, Leu308, Glu309, His310.
Ginsenoside RO	Pro159: 2.70 Å; Arg240: 3.14 Å Ser242: 3.15 Å; Gly243: 3.00 & 2.73 Å Arg298: 2.99 & 2.95 Å; Leu308: 3.02 Å Gly311: 3.02 Å	Lys160, <u>Val163</u> , Phe241, <u>Leu245, Lys248, Glu309</u> , His310.
Calbistrin C	Pro159: 3.13 Å; Lys160: 3.04 & 3.34 Å <u>Gln238: 2.84 Å</u> ; Gly243: 3.07 Å Leu308: 3.24 Å; <u>His310: 3.09 Å</u>	<u>Val163, Phe241, Ser242, Leu245, Lys248, Glu309</u> .

**Table 3.** Pharmacokinetics and drug likeness properties of potential ligands

No	Compounds	MW (<500g/mo)	HA (≤10)	HD (≤5)	MR	MLOGP	Yes/No
1	Hesperidin	610.56	15	8	141.41	-3.04	NO
2	Cucurbitacin	498.65	6	2	138.22	2.24	YES
3	Ginsenoside Rh	622.87	8	6	172.26	2.55	NO
4	Ginsenoside Ro	957.11	19	11	234.00	-1.41	NO
5	Calbistrin C	542.66	8	4	150.58	2.15	NO

**Note:** MW=Molecular weight; HD=Hydrogen donors; HA=Hydrogen acceptors; LogP=High Lipophilicity; MR=Molar refractivity

10, Log P less than 5, and molar refractivity between 40-130 [19]. Among those criteria, both of H-bond donor and acceptor contributed a crucial function for determining the specificity of ligand binding. Therefore, the drug compound could be assured to bind into specific target [20,21]. Re-

sult showed that only cucurbitacin which accomplished all the criteria (Table 3). It demonstrated by each criteria which belong to the Lipinski rule of five standard. Moreover, toxicity of all potential ligands were investigated.

Analysis of pharmacological activity showed

**Table 4.** Pharmacological activity of potential ligands

No	CID	Compounds	Pa score	Pi score	Activity
1	10621	Hesperidin	0.846	0.003	Antioxidant
			0.487	0.039	Immunostimulant
			0.193	0.102	Antiviral
2	119287	Cucurbitacin	0.286	0.101	Antiviral
			0.275	0.029	Antioxidant
3	119307	Ginsenoside RH2	0.900	0.004	Immunostimulant
			0.660	0.004	Antioxidant
			0.237	0.068	Antiviral
4	11815492	Ginsenoside RO	0.912	0.003	Immunostimulant
			0.686	0.004	Antioxidant
			0.303	0.035	Antiviral
5	6474046	Calbistrin C	0.251	0.036	Antioxidant
			0.172	0.131	Antiviral

**Table 5.** Toxicity class of potential ligands

No	CID	Compounds	LD <sub>50</sub> (mg/kg)	Tox Class	Acc (%)
1	10621	Hesperidin	12000	6	72.9
2	119287	Cucurbitacin	100	3	68.07
3	119307	Ginsenoside RH2	4000	5	70.97
4	11815492	Ginsenoside RO	3220	5	72.9
5	6474046	Calbistrin C	1190	4	100

that most of all selected compound had ability as an antiviral and immunostimulant. The predicted activity level was varied based on the probability of activity (Pa) score. Ginsenoside RH2 and ginsenoside RO had slightly higher of potential activity as antiviral as compared with the control (Calbistrin C). In brief, Ginsenoside RH2 and ginsenoside RO had Pa score about 0.237 and 0.303 while calbistrin c had Pa score about 0.172. Further interesting result exhibited that hesperidin, ginsenoside RH2, and ginsenoside RO had function as immunostimulant with Pa score 0.487, 0.900, and 0.912, respectively. Whilst calbistrin C had lack of immunostimulant activity (Table 4).

Score of Pa demonstrated the activity level of selected compound based on the study which held by related research. Score of Pa < 0.7 suggested high potential of compound, while  $0.5 < Pa < 0.7$  exhibited moderate potential of compound, and Pa < 0.5 showed poor potential of compound [22]. Therefore, it demonstrated that hesperidine, ginsenoside RH2, and ginsenoside RO had a potential function as candidate of antiviral and immunostimulant for Ebola virus disease treatment. It is in line with the pathology of Ebola virus which started by targeting and damaging the immune cells [4].

Analysis was conducted by using ProTox-II



webserver which helped to determine the toxicity class of each ligand. Result showed that all of ligands had different toxicity class. Hesperidin belongs to the higher toxicity class with LD<sub>50</sub> 12.000 mg/kg, while cucurbitacin belongs to the lowest toxicity class with LD<sub>50</sub> 100mg/kg. It could be concluded that hesperidin administration is estimated safer than cucurbitacin. However, all of those potential ligands had possibility to be developed as drug compound (Table 5).

#### 4. Conclusion

Ebola virus diseases is manifestation of disease which caused by infection of Ebola virus. It consists of various part of body structure, including Ebola virus nucleoprotein (EBOV NP) which had essential function for viral replication. Sixty five natural products or secondary metabolite derived from various traditional medicinal plants in Indonesia is analyzed to identify the most potential candidate for antiviral drug development. Result showed that there are four secondary metabolites with the lowest binding affinity score as compared to the Calbistrin C as reference compound, such as hesperidin, cucurbitacin, ginsenoside RH2, and ginsenoside RO. Further analysis including pharmacokinetics, drug likeness, pharmacological activity, and toxicity analysis also showed that all those four compounds are the most potential candidate for antiviral drug development. It could be collected from citrus, tea, and cucurbitaceae plants.

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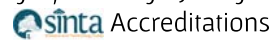
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