in silico centella asiatica

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Submission date: 28-Feb-2022 12:36AM (UTC+0000)
Submission ID: 1772270940
File name: JAdvPharmTechRes123261-4625164_125051_compressed.pdf (635.34K)
Word count: 3792
Character count: 20896

ORIGINAL ARTICLE

In silico identification of natural products from *Centella asiatica* as severe acute respiratory syndrome-coronavirus 2 main protease inhibitor

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J. Adv. Pharm. Technol. Res.

ABSTRACT

Severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) main protease (S-CoV-2 Mpro) is one of the main targets in designing antiviral against SARS-CoV-2. *Centella asiatica* contains several triterpenoids, polyacetylenes, and benzoic ester derivative with various biological activities including anti-inflammation and antiviral. Triterpenoids from *C. asiatica* could act as inhibitors of S-CoV-2 Mpro. The main objective of this study was to identify potential natural products from *C. asiatica* as S-CoV-2 Mpro inhibitor with better pharmacokinetic through in silico molecular docking method. : As much as 11 compounds from *C. asiatica* were docked with S-CoV-2 Mpro (PDB ID: 6LU7) using AutoDock v4.2.6. Pharmacokinetic parameters of these compounds were assessed using SwissADME (free access webserver). Molecular docking results of 11 natural products indicated that asiatate 6 and asiatate 10 have strong interaction with quite similar binding free energy compared to native ligand (–9.00 and–9.58 kcal/mol compared to –9.18 kcal/mol, respectively) with proper interaction to the catalytic dyad (His41 and Cys145). Pharmacokinetic analysis revealed that asiatate 4, asiatate 10, and asiatate 11 have poor pharmacokinetic properties. These results indicated that asiatate 6 could be recommended for further study as S-CoV-2 M^{pro} inhibitor.

Key words: Asiaticoside, coronavirus disease-2019, isothankunic acid, molecular docking, polyacetylenes, triterpenoids

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Submitted: 08-Dec-2020 **Revised:** 08-Feb-2021
Accepted: 28-Mar-2021 **Published:** 16-Jul-2021

Access this article online

Quick Response Code:

Website: www.japtr.org

DOI: 10.4103/japtr.JAPTR_297_20

INTRODUCTION

Coronavirus disease-2019 outbreak is caused by severe acute respiratory syndrome coronavirus-2 (S-CoV-2), a betacoronavirus strain. Development of antiviral drugs has been performed by targeting certain proteins either in the virus including structural or nonstructural proteins in S-CoV-2 or host targets.[1]

Main protease (M^{pro}) or 3-chymotrypsin-like protease is a nonstructural protein that has a significant role in viral replication and governing the response of the cell

How to cite this article: Maya PG, Mahayasih W, Harizal, Herman, Ahmad I. *In silico* identification of natural products from *Centella asiatica* as severe acute respiratory syndrome-coronavirus 2 main protease inhibitor. J Adv Pharm Technol Res 2021;12:261-6.

host. Together with papain-like protease, M^{pro} cleaves and transforms two large polyproteins (pp1a and pp1ab) translated from the viral RNA selectively at the Leu-Gln↓(Ser, Ala, Gly) cleavage site.[2] Due to its crucial role and specific cleavage site, inhibiting the activity of M^{pro} enzyme would stop viral replication with no undesired toxic effect on human.

Several potential synthetic drugs have been evaluated clinically against S-CoV-2 such as ritonavir/lopinavir[3] and cobicistat/darunavir.[4] However, these drugs still have not been approved by FDA for S-CoV-2 patients due to several limitations such as poor pharmacokinetic,[3] low effectivity,[4] and certain adverse effects.[5] On the other side, repurposing of various classes of natural products in several herbs for S-CoV-2 M^{pro} inhibitor also showed promising results. These repurposings were mainly conducted through *in silico* approaches such as terpenoids from *Cacospongia mycofijiensis*,[6] diterpenoids and bioflavonoids from *Torreya nucifera*,[7] glycosylated flavonoids from various herbs, and saponins and tannins from various herbs.[8]

Centella asiatica is a traditional herb from Southeast Asia that is widely used as medicines, cosmetics, foods, and beverages. This herb is known with different local names in different countries such as tapak kuda (Indonesia), pegaga (Indonesia and Malaysia), and gotu kola (Sri Lanka). *C. asiatica* contains various classes of active compounds (triterpenes, polyacetylenes, carotenoids, flavonoids, etc.) with different pharmacological activities including antioxidant, anti-inflammation, antidiabetic, and antimicrobial.[9] *C. asiatica* also has antiviral activity against several viral strain such as human immunodeficiency virus (HIV), hepatitis B virus (HBV), and herpes simplex virus (HSV).[10,11]

Among these classes of active compounds, aglycone and glycoside forms of triterpenoids were considered as the most active ingredients in this herb, especially for therapeutic purposes. Several triterpenoids also have been identified *in silico* as active S-Cov-2 inhibitors in several reports such as asiatic acid derivatives and asiaticoside derivatives.[12] In this report, we tried to identify potential triterpenoids, polyacetylenes, and benzoic ester derivatives from *C. asiatica* as S-CoV-2 M^{pro} inhibitor through molecular docking as part of repurposing of active ingredients in *C. asiatica*.

MATERIALS AND METHODS

Materials

Materials used in this investigation were 11 known compounds from *C. asiatica* obtained from various literatures[13,14] and receptor protein S-CoV-2 M^{pro} (PDB ID:6LU7). The *in silico* molecular docking study was conducted using Autodock v4.2.6 and AutodockTools (http://autodock.scrips.edu/), ChemOffice Pro v15.00 PerkinElmer, Python Molecular Viewer (PMV 1.5.6), Open Babel graphical user interface (GUI), and Discovery Studio Visualizer.

Native ligand and protein receptor preparation

Protein structure of S-CoV-2 M^{pro} complexed with N3 as native ligand at PDB 6LU7 (2.16 Å resolution) was obtained from the Protein Data Bank via website https://rcsb.org. Native ligand from each Protein Data Bank was separated using PMV 1.5.6. Receptor and native ligand were separated in PDBQT (.pdbqt) format using AutodockTools[15] and Open Babel GUI programs.[16]

Test ligands preparation

The structure of test ligands from *C. asiatica* was obtained from some literatures [as shown in Figure 1]. Preparation of ligands structure was performed using ChemDraw® Pro v15 and Chem3D® Pro v15 then process, as described by Wang *et al.*[17]

In silico molecular docking analysis

Autodock v4.2.6 (The Scripps Research Institute) was used for *in silico* molecular docking of 11 compounds from *C. asiatica* as S-CoV-2 M^{pro} inhibitor. Lamarckian parameters were used to perform the docking simulation. The grid box size and position were also validated to analyze the 11 known compounds from *C. asiatica* and visualized using Accelrys Discovery Studio Visualizer 4.0.

Pharmacokinetic properties analysis

Pharmacokinetic parameters of test and native ligands were predicted using SwissADME (http://swissadme.ch/).[18]

RESULTS

In silico molecular docking study

Inhibition activity of 11 natural products isolated *C. asiatica* against S-CoV-2 M^{pro} has been conducted through *in silico* molecular docking study. This investigation aimed to identify activity of S-CoV-2 M^{pro} inhibition based on the bonding form and interaction between the ligands and active site of receptor. The structure of S-CoV-2 M^{pro} consisted of 3 domains including domain I (residues 8–101), domain II (residues 102–184), and domain III (residues 185–200). Residue histidine 41 (His41) located in domain I and cysteine 145 (Cys145) located in domain II were the active sites of S-CoV-2 M^{pro}.[19]

Docking results of ligands-receptor were evaluated by verifying re-docking result of native ligand (N3) and S-CoV-2 M^{pro}. Re-docking verification was performed based on the RSMD value of lowest interaction energy between backbone atoms and active site of S-CoV-2 M^{pro} of 1.112 Å (with Gibbs free energy of –6.91 kcal/mol at 86 clusters) and 0.978 Å (with Gibbs free energy of –9.18 kcal/mol at 36 clusters) for 100 runs with 2 Å RMSD tolerance, as described in Figure 2.

According to the interactions shown in Table 1, the interaction pattern of native ligand (N3)-amino acids located inside the active site after the re-docking was still similar to the interaction before the re-docking in which the native

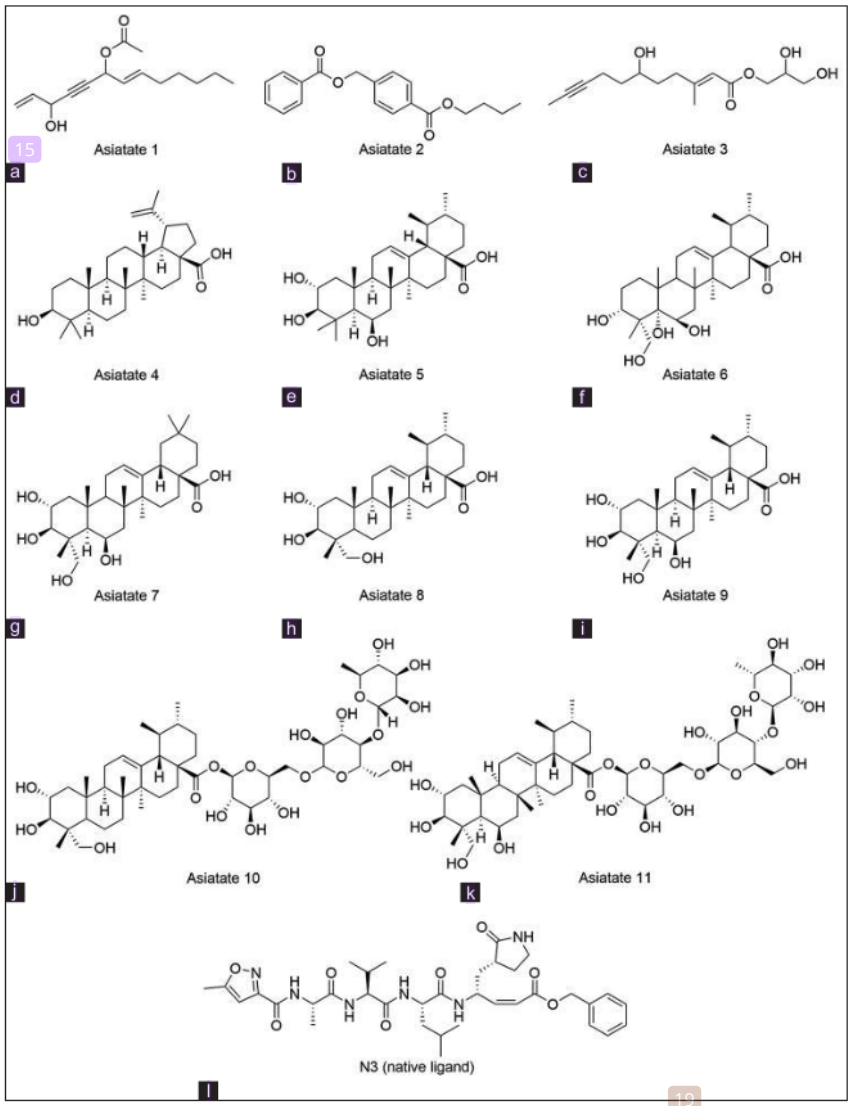

Figure 1: Structure of test and native ligands (a) centellin, (b) asiaticin, (c) cenetellicin, (d) betulinic acid, (e) madasiatic acid, (f) isothankunic acid, (g) terminolic acid, (h) asiatic acid, (i) madecassic acid, (j) asiaticoside, (k) madecassoside, (l) N3, native ligand

ligand (N3) had closely interacted with His41 in domain I dan Cys145 in domain II. Native ligand (N3) was formed pi-alkyl interaction with His41, covalent bonding with Cys145, and also interaction with other residues. Molecular docking results of 11 compounds obtained from *C. asiatica* indicated that asiatate 6 and asiatate 10 [Figure 3] have strong interaction with quite similar binding free energy to native ligand (–9.00 and –9.58 kcal/mol compared to –9.18 kcal/mol, respectively). Asiatate 11 even had stronger interaction with S-CoV-2 M^{pro} active site (binding free energy of –10.98 kcal/mol); however, it did not interact with His41 residue in domain I as one of the residues of catalytic dyad.

Pharmacokinetics properties analysis

Pharmacokinetics properties of native and test ligands were analyzed using free web server SwissADME.[18] Molecular weight of 11 compounds showed a wide range of values from 250 to 1000 g/mol. In this range, 9 compounds (asiatate 1–9) have MW below 505 g/mol which are easy to be transported, diffused, and absorbed in the human body, while 2 compounds (asiatate 10–11) have about 950 g/mol which are hard to be distributed inside the body. These also could be figured out from high topological polar surface area (>140 Å^2),[20] low bioavailability score (0.17 for small molecules that fail to pass rule of five),[21] low gastrointestinal absorption,

Table 1: Characteristics of ligands-receptor interactions

Compound	Binding free energy (kcal/mol)	Inhibition constant	Interaction
Asiatate 11	−10.98	8.95 nM	Gln189, His172, Gly170, Pro168, Leu167, Glu166, Met165, His164, His163, Cys145, Ser144, Gly143, Asn142, Leu141, Phe140, Met49, Thr45, Thr26, Thr25, Thr24
Asiatate 10	−9.58	95.01 nM	Gln189, His172, Pro168, Glu166, Met165, His164, His163, Cys145, Gly143, Asn142, Leu141, Phe140, Met49, His41, Leu27, Thr26, Thr25, Thr24
N3	−9.18	186.57 nM	Ala191, Thr190, Gln189, Arg188, Asp187, His172, Pro168, Leu167, Glu166, Met165, His164, His163, Cys145, Ser144, Gly143, Asn142, Leu141, Phe140, Tyr54, Met49, His41, Thr26
Asiatate 6	−9.00	254.38 nM	Gln192, Thr190, Gln189, Arg188, Pro168, Leu167, Glu166, Met165, His164, His163, Cys145, Ser144, Gly143, Asn142, Leu141, Met49, His41, Leu27, Thr25
Asiatate 4	−8.89	303.25 nM	Gln189, Glu166, Met165, His164, His163, Cys145, Asn142, Met49, Thr45, His41, Leu27, Thr26, Thr25, Thr24
Asiatate 5	−8.07	1.21 μM	Gln192, Thr190, Gln189, Arg188, Pro168, Leu167, Glu166, Met165, His164, Cys145, Ser144, Gly143, Asn142, Leu141, Met49, His41, Leu27
Asiatate 7	−8.02	1.33 μM	Gln192, Ala191, Thr190, Gln189, Arg188, Pro168, Leu167, Glu166, Met165, His164, Cys145, Ser144, Gly143, Asn142, Met49, His41, Leu27
Asiatate 3	−7.88	1.67 μM	Gln192, Thr190, Gln189, Arg188, Pro168, Leu167, Glu166, Met165, His164, His163, Cys145, Ser144, Gly143, Asn142, Leu141, Phe140
Asiatate 1	−7.84	1.79 μM	Gln189, His172, Glu166, Met165, His164, His163, Cys145, Ser144, Gly143, Asn142, Leu141, Phe140, Met49, His41, Leu27, Thr26, Thr25, Thr24
Asiatate 2	−7.71	2.24 μM	Gln192, Thr190, Gln189, Arg188, Pro168, Leu167, Glu166, Met165, Cys145, Ser144, Gly143, Asn142, Leu141, Met49, His41, Leu27
Asiatate 8	−7.63	2.56 μM	Gln189, Arg188, Asp187, Glu166, Met165, His164, Cys145, Gly143, Asn142, Met49, His41, Leu27, Thr26, Thr25, Thr24
Asiatate 9	−7.52	3.07 μM	Arg188, Asp187, Glu166, Met165, His164, Cys145, Gly143, Asn142, Met49, Ser46, His41, Leu27, Thr26, Thr25, Thr24

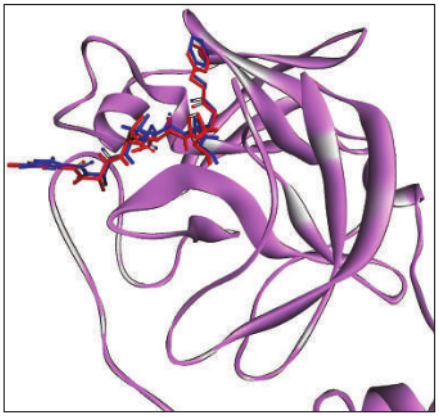

Figure 2: Native ligand (blue) and native ligand re-docked (red) comparisons

and no blood–brain barrier (BBB) permeation values that indicated that asiatate 10 and asiatate 11 have poor pharmacokinetic properties. The remaining molecules (asiatate 1–asiatate 9) showed better pharmacokinetic parameters except for asiatate 4 with high lipophilicity (log *P* >5) which would cause rapid metabolic turnover, low solubility, and poor absorption.[22]

DISCUSSION

C. asiatica is a traditional herb containing various active compounds such as terpenoids and polyacetylenes. with antiviral activity against certain viruses such as HIV, HSV, and HBV.[10,11] In this report, it was revealed that several active compounds might have anti-S-CoV-2 activity by inhibiting S-CoV-2 M^{pro}.

In general, all of the test ligands showed high affinity toward S-CoV-2 M^{pro} with binding free energy range from –7.52 to –10.98 kcal/mol; however, only asiatate 6 (E_{Bind} = –9.00 kcal/mol) and asiatate 10 (E_{Bind} = –9.58 kcal/mol) showed the highest affinity with proper interaction with His41 and Cys145 as catalytic dyad residues. Although both asiatate 6 and asiatate 10 were triterpenoid derivatives, they interacted with amino acid residues in the active site of S-CoV-2 M^{pro} with different parts of molecules. Asiatate 6 (a nonglycosylated triterpenoid) entered the active site and interacted with the residue through its pentacyclic triterpenoid backbone, while asiatate 10 (a glycosylated triterpenoid) entered the active site through glycosides moiety. This phenomenon was probably due to the bigger size of the asiatate 6 and asiatate 10 compared to the size of active site. Higher affinity of asiatate 10 and asiatate 11 toward S-CoV-2 M^{pro} was also probably due to the formation

of many hydrogen bonds between amino acids residues and glycoside moiety.[23]

From pharmacokinetic viewpoint, asiatate 6 showed better pharmacokinetic properties than asiatate 10 in which the later molecule violated 3 of 5 Lipinski rules, while the former one only violated 1 of 5 Lipinski rules. Other poor pharmacokinetic parameters also showed for asiatate 10 such as lower gastrointestinal absorption and smaller bioavailability score [Table 2]. This high affinity-poor pharmacokinetic properties of asiatate 10 also can be observed from glycyrrhizin which have the same structural features as asiatate 10.[24] From *in silico* molecular docking and pharmacokinetics analysis, it can be stated that asiatate 6 was the most recommended compound for further *in vitro* study.

Both asiatate 6 and asiatate 10 were pentacyclic triterpenoid derivatives. This class of compound showed a high affinity toward S-CoV-2 M^{pro} in some reports including several test ligands used in these investigations such as asiatic acid (asiatate 8) and asiaticoside derivatives (asiatate 10).[25,26] Other triterpenoid derivatives either from semisynthetic or natural also showed strong interaction including withaferin, acetylated asiatic acid,[25] soyasaponin I, glycyrrhizin,[24] and quinone-methide triterpenes.[26] From these reports, it was revealed that triterpenoid derivatives need special attention for S-CoV-2 M^{pro} inhibitor.

CONCLUSIONS

Of 11 natural products isolated from *C. asiatica*, asiatate 6 indicated high potency as S-CoV-2 M^{pro} inhibitor. Asiatate 6 has quite similar binding free energy with S-CoV-2 M^{pro} as compared to native ligand (N3) with proper interaction to the catalytic dyad residues. Pharmacokinetic parameters' analysis also revealed that asiatate 6 has good pharmacokinetic performance. From these results, asiatate

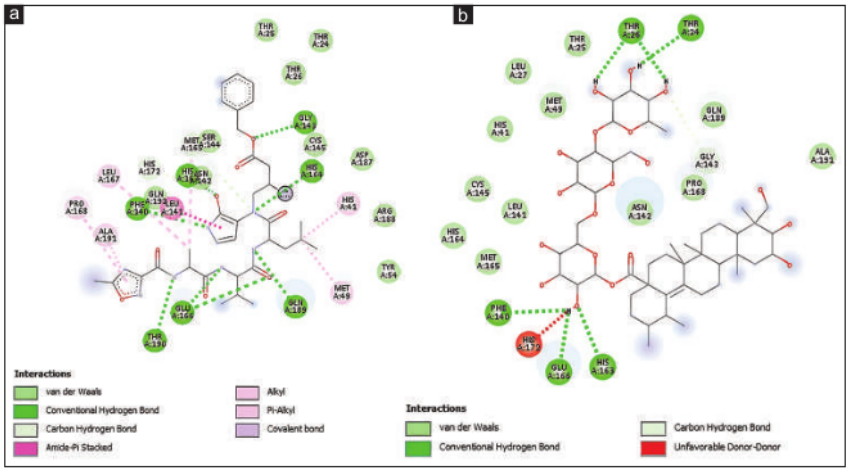

Figure 3: Three dimension of S-CoV-2 M^{pro} with (a) native ligand and (b) asiatate 10

Table 2: Pharmacokinetics properties of native ligand (N3) and test ligands

Ligands	E_{Bind}	MW	B_{rot}	H_{Don}	H_{Acc}	TPSA	log P	GI_{Abs}	BBB	NLV	BS
N3	−9.18	684.82	22	5	9	197.83	2.50	Low	No	2	0.17
Asiatate 1	−7.84	250.33	8	1	3	46.53	3.17	High	Yes	0	0.55
Asiatate 2	−7.71	312.36	9	0	4	52.60	4.13	High	Yes	0	0.55
Asiatate 3	−7.88	284.35	10	3	5	86.99	1.72	High	No	0	0.55
Asiatate 4	−8.89	456.71	2	2	3	57.53	6.14	Low	No	1	0.85
Asiatate 5	−8.07	488.70	1	4	5	97.99	4.27	High	No	1	0.56
Asiatate 6	−9.00	504.70	2	5	6	118.22	3.65	High	No	1	0.65
Asiatate 7	−8.02	504.70	2	5	6	118.22	3.87	High	No	1	0.56
Asiatate 8	−7.63	488.70	2	4	5	97.99	4.28	High	No	0	0.56
Asiatate 9	−7.52	504.70	2	5	6	118.22	3.62	High	No	1	0.56
Asiatate 10	−9.58	959.13	10	12	19	315.21	−0.30	Low	No	3	0.17
Asiatate 11	−10.98	975.13	10	13	20	335.44	−1.26	Low	No	3	0.17

E_{Bind}: Binding free energy (kcal/mol), MW: Molecular weight (g/mol), B_{rot}: Number of rotatable bonds, H_{Don}: Number of hydrogen bond donors, H_{Acc}: Number of hydrogen bond acceptor, TPSA: Topological polar surface area (Å^2), log P: Predicted octanol/water partition coefficient, GI_{Abs}: Gastrointestinal absorption, BBB: Blood-brain barrier permeation, NLV: Number of Lipinski rule violation, BS: Bioavailability score

6 could be recommended for further evaluation as S-CoV-2 M^{pro} inhibitor.

Financial support and sponsorship

This research was supported by Ministry of Research and Technology/National Research and Innovation Agency in funding aspect through Inter-Higher Education Collaborative Research grant with contract number 183/SP2H/AMD/LT/DRPM/2020.

Conflicts of interest

There are no conflicts of interest.

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