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MOLECULAR DOCKING ANALYSIS OF NATURAL PRODUCTS FROM *Centella asiatica* FOR INHIBITION OF RENIN

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ABSTRACT

Renin inhibitors derived from natural ingredients often belong to the saponin or polyphenol chemical class. Pegagan (*Centella asiatica*) is a natural plant in Indonesia that contains saponins and polyphenols. The active compounds of Pegagan include asiaticoside, madasiatic acid, madecassoside, madecassic acid, and asiatic acid. This study investigates the possible renin-inhibitory properties of phytochemicals from *Centella asiatica* using *in-silico* molecular docking. Using AutoDock v4.2.6, up to five *C. asiatica* compounds were docked with 2V0Z Renin with Inhibitor 10 (Aliskiren) in human subjects (Homo sapiens 6LU7). These compounds included asiaticoside, madasiatic acid, madecassoside, madecassid acid, and asiatic acid. SwissADME was used to evaluate these drugs' pharmacokinetic characteristics. The molecular docking results of 5 test ligands obtained affinity energy values from -8.7 kcal/mol to -10.4 kcal/mol. In contrast, the affinity energy value for the comparison ligand (aliskiren) is -9.0 kcal/mol. Madecasosside has an affinity energy value of -10.4 kcal/mol, asiaticoside of -9.6 kcal/mol and asiatic acid of -9.2 kcal/mol. Based on this energy affinity value, the active compound *C. asiatica* has the potential as a renin inhibitor. Pharmacokinetic analysis revealed that asiatic acid, madecassic acid, madasiatic acid, and asiatic acid have good pharmacokinetic properties. It may be concluded based on in silico molecular docking and pharmacokinetics investigation that the molecule most strongly suggested for additional in vitro renin inhibitor research was asiatic acid.

Keywords: Renin Inhibitor, *Centella asiatica*, Molecular Docking.

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INTRODUCTION

The RAAS, or renin-angiotensin-aldosterone system, is a group of hormone systems that work well together. Human blood pressure is mainly controlled by the renin-angiotensin system, which comprises renin, angiotensinogen (AGT), angiotensin-converting enzyme (ACE), and angiotensin receptors.[1] The highly specialized aspartic protease renin breaks the AGT between Leu10 and Val11, freeing the angiotensin I peptide at the N-terminus.[2] Angiotensin II, the primary physiologically active hormone, is created by ACE's subsequent processing of this peptide. It works by interacting with receptors. The breakage of AGT by renin is the rate-limiting phase in the renin-angiotensin cascade.[3] The 406 amino acids that make up the core structure of the renin precursor are divided into 20 and 46 amino acids for each pre- and pro-segment, respectively. Three hundred forty amino acids make up the 37 kDa weight of mature renin. Human renin has two mostly b-sheet domains in its crystal structure, connected by an axis roughly bifurcated in two. The two domains are separated by the active-site cleft, which covers eight residues of each substrate. One of the aspartic acid carboxylates needed for catalysis is present in every domain (Asp32 and Asp215). The inhibitors bind in an expanded configuration in every previous peptidic inhibitor-enzyme complex, changing the S4 subsites' position as the active site to the S2 subsites.[1] SRAA is one of the targets of action of antihypertensive drugs, including renin inhibitors, ACE inhibitors, angiotensin II receptor antagonists, and antagonists of aldosterone. Renin-inhibitors are antihypertensive drugs that act in the early stages of SRAA.[4] Aliskiren is non-peptide, administered orally, and currently is the only direct renin inhibitor used to treat hypertension. Aliskiren efficiently and specifically inhibits human renin. More so

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than in reaction to ACEIs and ARBs, aliskiren treatment causes a rise in plasma renin concentration. Since it is substantially below the 20 to 100-fold increase necessary to overcome 95% of renin suppression, the increase in plasma renin concentration does not result in a paradoxical rise in blood pressure.[4,5] Aliskiren is well tolerated in single or in combination doses. Side effects of aliskiren that commonly occur are angioedema on the face, extremities, lips, tongue, glottis, or larynx, diarrhea, headache, nasopharyngitis, fatigue, upper respiratory tract infections, and back pain.[5] Discontinuation of renin blockers did not cause rebound hypertension, as did ACE inhibitors and angiotensin receptor blockers. Renin-inhibitors also induce much greater renal vasodilation than ACE inhibitors.[6] Indonesia has various natural resources, both flora and fauna, many of which have not been used scientifically. This makes the authors interested in researching medicinal plants in Indonesia, which are considered to have acted as a renin inhibitor used in the treatment of hypertension. Renin inhibitors generated from natural substances often belong to the saponin or polyphenol chemical class.[7] Renin inhibitors from natural substances often belong to the saponin or polyphenol compound. Pegagan (*Centella asiatica*) is a natural plant in Indonesia that contains saponins and polyphenols. Since ancient times, Pegagan has been used empirically as a blood pressure-lowering drug, antibacterial, skin medicine, and medicine for nervous disorders. Pegagan is widely used as a natural medicine and contains various active compounds, the active compound being triterpenoid saponins. The active compounds of triterpenoid saponins include asiaticoside, madasiatic acid, madecassoside, madecassic acid, and asiatic acid.[8] Computer-aided drug discovery (CADD) techniques have transformed drug discovery methods. In-silico methods can now be used for anything from medication target identification to evaluating the possible toxicity of the drugs. They provide the convenience of being both time and cost-efficient. This method is employed to start the search for new drug compounds and make it easier to improve the activity of the parent compound. CADD has effectively introduced novel medicinal molecules for various ailments, including HIV-1 inhibitors (atazanavir, saquinavir, and indinavir), and anticancer medicines. This study investigates the possible renin-inhibitory properties of phytochemicals from *Centella asiatica*, such as asiaticoside, metastatic acid, madecassoside, madecassic acid, and asiatic acid by in silico methods.[9]

EXPERIMENTAL

Material

The tools employed in this experiment include a personal computer with an Intel Core i5-1005G1 processor with Windows 11 operating system and 8 GB RAM. The software used for the docking simulation includes MGL Tools 1.5.7 (Autodock Vina 1.1.2 and Autodock Tools 1.5.7), Marvin Sketch 22.2, and Discovery Studio Visualizer 21.1.0.20298. Renin inhibitor protein structure (Aliskiren) with PDB ID code: 2V0Z obtained from https://www.rcsb.org/ (PDB) and using the ligand structure used from the active compound C. asiatica, namely asiaticoside, madasiatic acid, madecassoside, madecassic acid, and asiatic acid obtained from https://pubchem.ncbi.nlm.nih.gov.

Macromolecular Structure Preparation

The macromolecule used in this study is the human renin protein receptor (GDP: 2V0Z), which was received through the PDB website (https://www.rcsb.org/), then downloaded in pdb format. Protein macromolecules are separated from other molecules that are not needed. If protein macromolecules have been isolated from unnecessary molecules, the next step is to add hydrogen atoms using auto dock tools.[10,11]

Ligand Preparation

The ligands used are *C. asiatica* compounds: asiaticoside, madasiatic acid, madecassoside, madecassic acid, and asiatic acid. Ligand preparation begins by downloading the 2D structure in sdf. the format from the PubChem webpage (https://pubchem.ncbi.nlm.nih.gov/). Furthermore, a 2D form is optimized into a 3D structure with the Marvinsketch program package, then saved in the mol2 file format.[12]

Molecular Optimization Using Autodock Tools 1.5.7

Optimization of macromolecular structures was conducted utilizing Autodock Tools 1.5.7. The optimization includes the addition of hydrogen atoms and the determination of grid box parameters. The grid box serves to show the active site of protein receptors. The next step involves selecting Grid and selecting a protein name to save as a pdbqt file.

Docking Method Validation

The redocking method confirmed the docking method. The method was validated using Autodock Tools 1.5.7 software. If the resultant RMSD is less than or equal to 2 and the receptor can be used for molecular docking, the method's correctness has been confirmed.

Molecular Docking Using Autodock Vina

The structure of the renin receptor and the ligands are then used in the docking procedure with Autodock Vina. Each test and comparison ligand is docked to the renin receptor. The docking process is carried out using the coordinates and grid boxes that have been determined. The docking results produce affinity energy values observed in the ligand binding area to the renin receptor.

Pharmacokinetic Properties Analysis

SwissADME (http://swissadme.ch/) was implemented to estimate test and native ligand pharmacokinetic characteristics.[13]

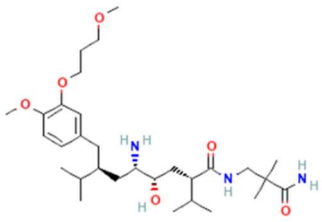
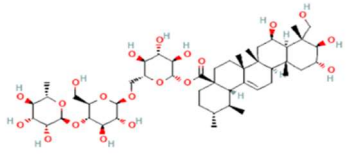
Data Analysis

The molecular docking data was analyzed by looking at the differences in affinity energy values and the interaction of amino acid residues from protein receptors, comparison ligands, and test ligands. Visualization was performed using the Discovery Studio Visualizer to see the interaction of amino acid residues.

RESULTS AND DISCUSSION

This study's initial process of in silico study begins with preparing protein macromolecules to be used. In this preparatory stage, the macromolecular structure of the protein used was downloaded from PDB on http://www.rcsb.org/ site. The protein used in this study was 2V0Z, Renin with Inhibitor 10 (Aliskiren) in humans (Homo sapiens). This protein macromolecule is bound to a ligand, i.e., aliskiren. In this study, re-docking was carried out five times with different sizes. The grid box size used is 35×35×35, with coordinates center_x = 7.246, center_y = 46.072, center_z = 69.017, and spacing (Angstrom) = 1. The Gibbs free energy number for this grid box size is -9.0 kcal/mol, while the RMSD number is 1.888. If the RMSD value is less than 2, the method is approved. Table 1 summarizes the amino acid residues on the renin protein interacting with the test and native ligands (aliskiren). The amino acid interaction in the test and native ligands occurs through hydrogen, and van der Waals bonds can be seen in Table-2.

Table-1: Amino Acid Residues on the Renin Protein that Interact with the Test and Native Ligands (aliskiren)

Ligand	Gibbs free energy (kcal/mol)	Amino acid residues
Aliskiren 	-9.0	Asp32, Ap215, Ala303, Ala218, Ala115, Arg74, Gly34, Gly217, Gln13, Gln128, , Ile130, Ile291, Leu114, Leu213, Phe112, Phe117, Ser35, Ser36, Ser76, Ser219, Thr12, Thr77, Thr216, Thr295, Tyr14, Tyr75, Tyr155, Val20, Val130, Pro111
Madecassoside 	-10.4	Asp32, Asp215, Asp244, Ala115, Ala218, Ala288, Arg240, Gln13, Gln34, Gly217, His287, Leu 114, Leu241, Met289, Phe112, Phe117, Phe242, Pro111, Ser35, Ser219, Thr12, Thr77, Tyr75, Tyr220, Val120
Asiaticoside	-9.6	Asp32, Asp215, Ala115, Ala300,Arg74, Gln13, Gly34, His287, Ile130, Ile291, Leu114, Leu213, Met298, Phe112, Phe117, Phe242, Pro111, Ser35, Ser36,

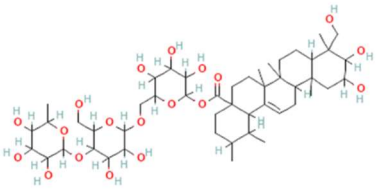
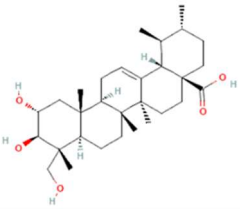
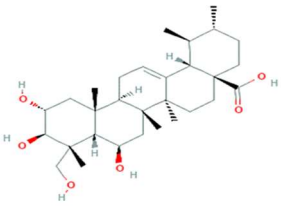
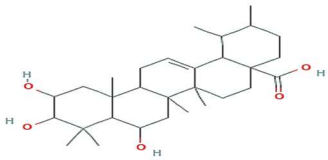
		Ser219, Ser222, Thr77, Thr295, Thr298, Tyr75, Tyr77, Tyr220
Asiatic acid 	-9.2	Asp215, Ala218, Gln13, Gly78, Gly217, His287, Leu114, Met289, Phe112, Phe117, Phe242, Pro111, Ser219, Thr12, Thr77, Tyr9. Tyr75, Tyr220
Madecassid acid 	-8.8	Asp32, Ala115, Ala218, Ala288, Gln13, Gly217, His287, Met289, Phe117, Phe242, Pro111, Ser219, Thr12, Thr77, Tyr220, Val30, Val120
Madasiatic acid 	-8.7	Asp32, Ala115, Gln13, Gly78, Gly217, His287, Leu114, Phe112, Phe117, Ser219, Pro111, Thr12 Thr77, Tyr75, Tyr220, Val30, Val120

Table-2: Amino Acid Residues on the Renin Protein That Form Hydrogen and Van Der Waals Bonds With Native and Test Ligands

No	Ligand	Hydrogen bond	Van der Walls Bond
1	Aliskiren	Gln128, Gly34, Gly217, Ser76	Pro111, Ser219, Thr216, Arg74, Ala218, Ala303, Gln13, Ile130, Leu213, Phe112, Ser35, Thr12, Thr77, Thr: 295, Tyr14, Tyr155,
2	Madecassoside	Ala288, Asp215, Leu241, Phe242, Ser219, Thr77	Ala115, Ala218, Arg240, Asp32, Asp244, Gln13, Gly34, His287, Leu114, Met289, Phe112, Pro111, Ser35, Thr12, Tyr220, Val120
3	Asiaticoside	Arg 74, Gly 34, Ser76, Ser219, Thr 77, Tyr 220	Asp215, Ala218, Ala300, Asp32, Gln13, His287, Ile130, Ile291, Leu213, Met289, Phe242, Pro:292, Ser35, Ser222, Thr295, Thr298, Tyr220
4	Asiatic acid	Gln13	Asp215, Ala218, Gly78, Leu114, Met289, Phe112, Phe242, Ser219, Thr12, Thr77, Tyr9, Tyr75, Gly217
5	Madecassic acid	Ser219	Asp32, Ala115, Ala218, Ala288, Gln13, Gly217, Met289, Phe242, Thr12, Thr77, Tyr220
6	Madasiatic acid	-	Asp32, Ala115, Gln13, Gly78, Gly217, Ser219, Thr12, Thr77, Tyr75, Tyr220

The pathophysiology of hypertension is fundamentally influenced by the renin-angiotensin-aldosterone system (RAAS). The component in SRAA is renin. Renin is synthesized and stored as the inactive form, prorenin, in the juxtaglomerular apparatus of the kidney. Angiotensinogen, a globulin component of another plasma protein, is the substrate with which renin's enzyme reacts to create angiotensin, a 10-amino acid

peptide.[14] Angiotensin receptor blockers (ARBs) and ACEIs are two frequently prescribed antihypertensive drugs. The two drugs work by controlling SRAA. However, ACEI and ARB have not fully effective because it produces an incomplete suppressive effect of SRAA. This thing ultimately limits the therapeutic potential of both drugs.[15] Renin inhibitors are being developed as an antihypertensive medication that can block at the maximum level in the SRAA. The angiotensin type 1 (AT-1) receptor is not activated because renin inhibitors prevent the synthesis of angiotensin I and angiotensin II.[4] *Centella asiatica (L.)* is a plant frequently used as a traditional medicine to treat several ailments, such as hypertension and cardiovascular disease. Asiaticoside, brahmoside, and madecassic acid are only a few of the pentacyclic triterpenoids found in *C. asiatica*. Other components, including centellose, centelloside, and madecassoside are also present. Triterpenes, particularly asiaticoside, madecassoside, Asiatic acid, and madecassic acid are the most important chemical components for pharmacological activity.[16] *C. asiatica* positively impacts cardiovascular illnesses. Asiaticoside and Asiatic acid are essential substances that have an impact on the cardiovascular system.[17] Based on the validation of the molecular docking method between the aliskiren ligand and renin protein, the RMSD value was 1.888. Ligands docked on the protein renin were analyzed based on the affinity energy value and visually by looking at the pose and residue of the renin protein that interacts with each ligand. The more negative the affinity energy value, the more stable the conformation formed, while an enormous affinity energy value indicates that the complex formed is less stable. The molecular docking results of 5 test ligands, namely asiaticoside, madasiatic acid, madecassoside, madecassic acid, and asiatic acid, obtained affinity energy values in the range of -8.7 kcal/mol to -10.4 kcal/mol. In contrast, the affinity energy value for the comparison ligand (aliskiren) is -9.0 kcal/mol. Madecasosside has an affinity energy value of -10.4 kcal/mol, asiaticoside of -9.6 kcal/mol and asiatic acid of -9.2 kcal/mol. Based on this energy affinity value, the active compound *C. asiatica* has the potential as a renin inhibitor. According to human renin crystal structures, this enzyme is formed by two primarily b-sheet-based domains joined by a doubled axis. The active-site cleft, which spans eight residues of each substrate, divides the two domains. Each domain contributes a single aspartic acid carboxylate (Asp32 or Asp215) to the catalysis, with an extended configuration at the active site's S4 through S2 subsites.[2] Renin, an aspartic proteinase, catalyzes the breakdown of the Leu10-Val11 peptide link in angiotensinogen. It releases decapeptide angiotensin I as the first rate-limiting stage in the renin-angiotensin pathway. Contrary to the angiotensin-converting enzyme (ACE), which can be inhibited by the serine proteinase chymase and as well as being potent against other peptides like bradykinin, renin is a vital and particular enzyme that can only be produced by angiotensinogen.[18] A protein with 406 amino acid residues serves as the precursor to renin. Signal peptide sequence residues 1-23 are broken down into mature 340 amino acid residue renin by cleavage of residues 24-66. In addition to 29 antiparallel sheets, three bridges, four helices, 2 γ helices, and 18 twists. Renin also has secondary structural components. Its most striking structural characteristic is the antiparallel sheet that creates the two identical renin lobes. The parts of renin outside and inside have more hydrophilic and hydrophobic residues, respectively. The hydrophobic pocket in the active site, which enables substrate binding, is the most crucial structure. Renin has two crucial aspartate residues in its active site. Two catalytic motifs follow the two aspartate residues in renin. Additionally, the active site of renin is revealed or concealed by an active site flap, a hairpin-shaped structure that opens and shuts.[18,19] Aliskiren is a hydrophilic chemical. Aliskiren binds to renin and occupies a position in the hydrophobic S1, S1', S2, and S3 domains. Aliskiren primarily resides in the $S3^{SP}$ region, which is both hydrophobic and hydrophilic and significantly increases binding affinity. Multiple renin residues interact with the aliskiren. Both aspartate 32 oxygens are hydrogen bonded by the hydroxyl group. The oxygen atom of aspartate 32 and the carboxylic acid group of glycine 217 create a hydrogen connection through the amine group. The secondary amine group of tyrosine 14 builds a hydrogen interaction with the methoxy group in the S3 hydrophobic area. The secondary amine of serine 76 forms a hydrogen bond with the amide group. Additionally, in the S2' hydrophobic pocket, the terminal amide forms a hydrogen connection with arginine 74.[18] For all protease inhibitors, the ability to bind to the catalytic aspartate residues is essential. Every renin inhibitor exhibits interactions with either Asp 32 or Asp 215 of the renin's aspartate residues.[20] Madecasosside and asiaticoside interaction with the amino acid residues of Asp32 and Asp 215, similar to aliskiren (Table 1). Aliskiren occupies four of the active site pockets (S3, S1, S1', S2), while madecassoside and asiaticoside occupy four (S3, S2', S1', S2') and two pockets (S3, S2 and S2'), respectively. The molecular docking

results for aliskiren showed the presence of amino acid residues that play an essential role in renin binding. The residues were Thr12, Gln13, Pro111, Leu114, Ala115, Phe117, and Ser219 in the S3 pocket. Aliskiren does not have amino acid residues in the S2 pocket. The amino acid residues Leu213, Ser76, Thr 295, Gly217, Asp215, and Ile291, are present in S1' pocket. The amino acid residues Arg74, Gly34, Gln128, Ile130, Tyr75, and Ser35, are present in the S2' pocket, which is also essential for tight binding. Aliskiren has hydrogen interactions on amino acid residues Gln128, Gly34, Gly217, Ser76, and van der Walls interactions on amino acid residues Arg74, Ala303, Gln13, Ile130, Leu213, Phe112, Ser:35, Thr12, Thr77, Thr295, Tyr14, and Tyr155 (Table-1). The molecular docking results on the madecassoside compound showed the presence of amino acid residues that play an essential role in renin binding. The amino acid residues were Thr12, Phe117, Pro111, Phe112, Leu114, Ala115, Ser219, and Gln13 in the S3 pocket, Met289 in the S2 pocket, Asp215, Gly217 in the S1' pocket, Ser35, Tyr75 in the S2' pocket. Hydrogen bonds bind the amino acid residues to Ala288, Asp215, Leu241, Phe242, Ser219, Thr77, and van der Walls bonds to Ala115, Ala218, Arg240, Asp32, Asp244, Gln13, Gly34, His287, Leu114, Met289, Phe112, Pro111, Ser35, Thr12, Tyr220, and Val120. In comparison, molecular docking results on asiaticoside compounds showed the presence of amino acid residues that played an essential role in renin binding. The amino acid residues were Gln13, Pro111, Phe112, Leu114, Ala115, Phe117, Ser219 in pocket S3, Ser222, Met298 in pocket S2, Leu213, Asp215, Thr295, Thr298, Ala300 in pouch, and Arg74, Gly34, Ile130, Ser35, Tyr75 on bag S2'. Hydrogen bonds bind the amino acid residues to Arg74, Gly34, Ser76, Ser219, Thr77, Tyr 220, and van der Walls bonds to Ala218, Ala300, Asp32, Gln13, His287, Ile130, Ile291, Leu213, Met289, Phe242, Pro292, Ser35, Ser222, Thr295, Thr298, and Tyr220 (Table-2). Madecassoside, asiaticoside, and asiatic acid have more negative bond-free energy values than aliskiren. The quantity of free energy released upon interaction with the produced enzyme-ligand complex can be used to gauge the stability and effectiveness of non-covalent interactions. The bond-free energy data, which is negative and relatively small, indicates that the conformation of the ligand formed in the enzyme-ligand complex is stable.[21] So it can be analyzed that the three compounds formed an enzyme-ligand complex in a more stable conformation than the aliskiren and were able to inhibit the enzyme better than the aliskiren. The docking process's analysis is seen not only from the value of the bond energy but also from the interaction between the ligand and the enzyme, especially hydrogen bonds. Hydrogen bonding is defined as an intermolecular or intramolecular force between an atom with a high electronegativity and a hydrogen atom that is covalently bonded to an electronegative one.[21] Table-2 shows that Madecassoside, Asiaticoside, and asiatic acid compounds have 6, 6, and 1 hydrogen bonds with amino acids, respectively, while aliskiren has four hydrogen bonds. The hydrogen bonds formed by aliskiren tend to be less than madecassoside and asiaticoside, so it can be analyzed that madecassoside and asiaticoside have better inhibitory abilities than aliskiren. Table-3 shows the pharmacokinetic properties of the native ligand (aliskiren) and test ligands. Using ChemAxon's Marvin JS structure drawing tool, the structural characteristics of phytoconstituents found in *C Asistica* were put on the free web server SwissADME (http://www.swissadme.ch). The phytochemicals examined for their ADME properties included asiaticoside, madasiatic acid, madecassoside, madecassic acid, and asiatic acid. The Lipinski rule of five, which indicates that a molecule exhibits qualities comparable to medicines, was used as the basis for the drug-likeness investigation. If the molecule's molecular weight (BM) is 500 Daltons or less, the partition coefficient log P value, the number of hydrogen bond donors (HBD), and the number of hydrogen bond acceptors (HBA) are all less than 5. Then the compound is considered to belong to this condition.[22] From a pharmacokinetic viewpoint and based on Lipinski's rule of five, asiatic acid and madasiatic acid showed better pharmacokinetic properties than madecassic acid, madecassoside, and asiaticoside. Asiatic acid and madasiatic acid have zero violations of Lipinski's rule of five, while aliskiren and madecassic acid have one violation. The molecular weight of madasiatic and asiatic acid is less than 488 Da. If the molecular weight is more than 500 Da, the drug molecules cannot diffuse across the cell membrane. The more hydrophobic a molecule is, the higher the log P value. In the body, too-hydrophobic chemicals will be dispersed more widely and maintained extended in the lipid bilayer, reducing their capacity to bind to the target enzyme with the same degree of selectivity. As a result, they will have a higher level of toxicity.[23] A too-negative log P value is undesirable since it prevents the molecule from passing through the lipid bilayer membrane. According to the amount of hydrogen bond providers and acceptors, the energy needed for the absorption process increases as

hydrogen bonding capacity increases.[24] According to Lipinski's rule, some chemicals are soluble enough to diffuse passively across cell membranes.[23] Results from in silico molecular docking and pharmacokinetics study identified asiatic acid as the chemical that was most frequently recommended for more in vitro investigation.

Table-3: Native Ligand (aliskiren) and Test Ligand Pharmacokinetic Properties

Ligands	MW	Brot	HDon	HAcc	TPSA	log P	GIAbs	BBB	NLV	BS	PgP substrate
Aliskiren	551.76	20	4	7	146.13	4.15	low	no	1	0.55	yes
Madecassoside	975.12	10	13	20	335.44	1.87	low	no	3	0.17	yes
Asiaticoside	950.12	10	12	19	315.21	3.05	low	no	3	0.17	yes
Asiatic acid	488.7	2	4	5	97.99	3.2	high	no	0	0.56	yes
Madecassic acid	504.70	2	5	6	118.22	3.2	high	no	1	0.56	yes
Madasiatic acid	488.7	1	4	5	97.99	3.49	high	no	0	0.56	yes

MW: Molecular weight (g/mol), Brot: rotatable bonds number, HDon: hydrogen bond donors' number, HAcc: hydrogen bond acceptor number, TPSA: Topological polar surface area (Å2), log P: Octanol/water partition coefficient estimated, GIAbs: Gastrointestinal absorption, BBB: Blood-brain barrier permeation, NLV: The number of violations of the Lipinski rule, BS: score of bioavailability score; PgP: P-Glycoprotein

CONCLUSION

The active compound *C. asiatica has* the potential as a renin inhibitor Based on this energy affinity value. Pharmacokinetic analysis revealed that asiatic acid, madecassic acid, madasiatic acid, and asiatic acid have good pharmacokinetic properties. Asiatic acid was the substance most strongly suggested for more in vitro research for renin inhibitors, according to pharmacokinetics analysis and in-silico molecular docking.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

All the authors contributed significantly to this manuscript, participated in reviewing/editing, and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

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