RASĀYAN *J. Chem.*
Vol. 19 | No. 3 | 1808-1815 | July-September | 2026
ISSN: 0974-1496 | e-ISSN: 0976-0083 | CODEN: RJCABP
http://www.rasayanjournal.com
http://www.rasayanjournal.co.in

IN SILICO IDENTIFICATION OF LIMODISSIMIN A FROM KAWISTA (*Limonia acidissima* L.) AS A POTENTIAL ANGIOTENSIN-CONVERTING ENZYME INHIBITOR THROUGH BIOAVAILABILITY PREDICTION, MOLECULAR DOCKING, AND DYNAMICS SIMULATION

E.J. Astuti[1,2], M.A. Muchlisin[1,✉], D. Elvina[1], and A. Rafikayanti[1]
[1]Department of Pharmacy, University of Muhammadiyah Malang,
Malang-65145, (East Java) Indonesia
[2]Department of Apothecary, University of Muhammadiyah Malang,
Malang-65145, (East Java), Indonesia
✉Corresponding author: artabahmuchlisin@umm.ac.id

ABSTRACT
Kawista (Limonia acidissima) is a plant known for its potential pharmacological properties, including antihypertensive activity. This study aimed to evaluate the inhibitory potential of kawista secondary metabolites against angiotensin-converting enzyme (ACE) using an in silico approach. A total of 31 compounds were identified and screened for oral bioavailability using the BOILED-Egg model, resulting in 20 compounds with favourable pharmacokinetic properties. Molecular docking analysis revealed that limodissimin A (mol 17) exhibited the strongest binding affinity toward ACE (−9.09 kcal/mol; Ki = 215.73 nM), with key interactions involving Lys511, His353, and His513. Molecular dynamics simulations further confirmed the stability of the ACE–ligand complex, as indicated by lower RMSD, reduced structural fluctuations, and decreased solvent exposure compared to the apo protein. These findings suggest that limodissimin A is a promising candidate for ACE inhibition. Further experimental validation is required to confirm its potential as a natural antihypertensive agent.
Keywords: ACE, Limonia Acidissima, Kawista, Boiled-Egg, Molecular Docking, Molecular Dynamics.
RASĀYAN *J. Chem.*, Vol. 19, No.3, 2026

INTRODUCTION

Hypertension, or a high blood pressure, has become a significant global health problem and is known to be a significant risk factor for severe chronic kidney disease and cardiovascular diseases, including stroke and heart failure.[1] One widely used approach in controlling hypertension is the inhibition of the angiotensin-converting enzyme (ACE), converting angiotensin I to angiotensin II, a vasoconstrictor peptide that causes an increase in blood pressure.[2,3] Although existing ACE inhibitors have demonstrated clinical efficacy, their use is often associated with side effects such as angioedema and persistent cough, highlighting the necessity for alternative therapeutic agents.[4] In recent years, in silico approaches have become an invaluable tool in discovering and developing new drugs, enabling the rapid and cost-effective prediction of interactions between bioactive compounds and biological targets.[5] Techniques, such as molecular docking and molecular dynamics simulations, allow for detailed analysis of binding affinity, interaction stability, and conformational behaviour at the molecular level.[6] These computational methods provide valuable preliminary insights that can guide further experimental validation. Kawista or wood apple (*Limonia acidissima* L.) is one of the plants that has attracted the attention of researchers because it has been proven to have various pharmacological activities, including potential as an antihypertensive agent.[7,8] Previous studies, including our earlier network pharmacology analysis, have identified ACE as one of the key therapeutic targets associated with kawista.[9] However, despite these findings, there remains a lack of comprehensive studies that systematically identify specific secondary metabolites responsible for ACE inhibition, along with their pharmacokinetic properties and molecular stability. Therefore, this study aims to evaluate the secondary metabolites of kawista as potential ACE inhibitors

using an integrated in silico approach. Bioavailability prediction was performed to assess pharmacokinetic suitability, followed by molecular docking to determine binding affinity and interaction profiles. Molecular dynamics simulations will help us understand the stability and dynamics of ligand–protein complexes under dynamic conditions.[10,11] With this approach, we hope to reduce hypertension and improve global health outcomes.

EXPERIMENTAL

Tools

Molecular docking calculations were conducted using an Intel® 2.4 GHz Core i5-9300H processor, 8 GB RAM, and running a 64-bit Windows 10 operating system. Molecular dynamics simulations were conducted using an Intel® 2.90 GHz Core i5-10400 processor, 32 GB RAM, and under the same operating system environment. The software utilised in this study included Avogadro 1.2.0, BIOVIA Discovery Studio 2020, PyRx 0.8, and YASARA. Secondary metabolite data and supporting information were obtained from several publicly available databases, including Dr. Duke's Phytochemical and Ethnobotanical Database, KNApSAcK Family Database, PubChem, and the Protein Data Bank. Additional computational analyses were supported using SwissADME and ProteinsPlus web-based tools.

Identification and Bioavailability Prediction of Secondary Metabolites of Kawista

Secondary metabolites of kawista were collected from Dr. Duke's and KNApSAcK Databases. Inorganic constituents and fatty acids were excluded, and only relevant organic compounds were retained for SMILES notation retrieved from PubChem and subsequently evaluated for oral bioavailability using SwissADME through the BOILED-Egg model.[12,13] Compounds meeting the required criteria were selected for subsequent analysis.

Molecular Docking Simulations

The x-ray crystallography of ACE with captopril (CPT) as native ligand was retrieved from the Protein Data Bank (PDB ID: 1UZF).[14] The CPT was removed prior to docking preparation using BIOVIA Discovery Studio 2020. All secondary metabolite three-dimensional structures were downloaded from PubChem and prepared using Avogadro 1.2.0 to optimise their geometry using the MMFF94s force field.[5] Docking calculations were performed using PyRx 0.8 with the AutoDock 4.2.1 engine.[15] Docking validation was done by redocking CPT to ACE with 50 x 50 x 50 point and 0.375 Å space of grid box that was centered at CPT coordinates (x =41.171; y = 35.385; z = 45.092) and Lamarckian Genetic Algorithm (100 runs, 150 population size, 2500000 energy evaluations, 0.02 rate of gene mutation, and 0.8 rate of crossover) for docking algorithm.[16] The ligand conformation with the lowest free binding energy (ΔG) and inhibition constant (Ki) from the most favoured cluster was chosen for the next step.[17] Protein–ligand interactions were further analysed using ProteinsPlus.[18]

Molecular Dynamics Simulations

The compound exhibiting the most favourable docking result from Kawista was subjected to molecular dynamics simulations using YASARA with the AMBER14 force field over a 100 ns production run.[19] Then, the result was visualised with YASARA to see whether the ligand was still stable in its position. Then, the result was visualised with YASARA to see whether the ligand was still stable in its position. Furthermore, RMSD (Root Mean Square Deviation), Δ RMSD (Average RMSD), Rg (Radius of Gyration), and SASA (Solvent-accessible Surface Area) from MD simulation were analysed.

RESULTS AND DISCUSSION

Identification of Secondary Metabolites of Kawista

A total of 31 secondary metabolite compounds of kawista were identified by Dr. Duke's and KNApSAcK databases (Table-1). These databases provide comprehensive information on phytochemical composition, biological activity, and ethnobotanical relevance, including traditional medicinal formulations such as Kampo and Jamu.[20,21]

Bioavailability Prediction

Bioavailability prediction using the BOILED-Egg (Brain Or Intestinal EstimateD permeation) model showed that 20 out of 31 compounds were predicted to have favourable oral bioavailability. This model

estimates gastrointestinal absorption and blood–brain barrier permeability based on lipophilicity (WLogP) and electronic (topological polar surface area (TPSA)) parameters.[13,22]

Table-1: List of Secondary Metabolites Identified in Kawista

No.	Compound Name	Compound code
1	7-Methylporiol-Beta-D-Xylopyranosyl-D-Glucopyranoside	mol 1
2	Ascorbic-Acid	mol 2
3	Aurapten	mol 3
4	Bergapten	mol 4
5	17-Ethynylestra-1(10),2,4-triene-3,17-diol	mol 5
6	Estragole	mol 6
7	Isopimpinellin	mol 7
8	Marmesin	mol 8
9	Orientin	mol 9
10	Pectin	mol 10
11	Psoralen	mol 11
12	Riboflavin	mol 12
13	Stigmasterol	mol 13
14	Ursolic-Acid	mol 14
15	Vitexin	mol 15
16	Nb-Acetyl-Nb-Methyltryptamine	mol 16
17	Limodissimin A	mol 17
18	Integriquinolone	mol 18
19	Dihydroxyacidissiminol	mol 19
20	Dihydrosuberenol	mol 20
21	Acidissiminol epoxide	mol 21
22	Acidissiminol	mol 22
23	Acidissiminin epoxide	mol 23
24	Acidissiminin	mol 24
25	Acidissimin	mol 25
26	9",10"-Didehydrodihydroxyacidissiminin	mol 26
28	10,20-Dihydroxyeicosanoic acid	mol 28
29	1-(1H-Indol-3-yl)-3-methyl-2,3-butanediol	mol 29
30	(E)-Suberenol	mol 30
31	(+)-Lirioresinol B	mol 31

As shown in Fig.-1, compounds are predicted to have high gastrointestinal absorption located in the white region, while those in the yolk region are associated with blood–brain barrier penetration.[23] Only compounds within the white region were selected for further analysis. This filtering step ensures that only compounds with suitable pharmacokinetic properties are prioritised for molecular docking.

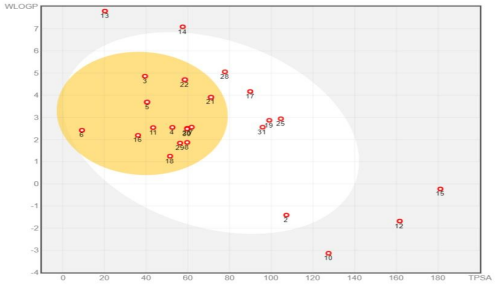

Fig.-1: BOILED-Egg Plot Illustrating the Bioavailability of Kawista Secondary Metabolites

Molecular Docking Simulation

The molecular docking study aimed to investigate the inhibitory potential of kawista secondary metabolites against ACE, using established inhibitors (CPT, LIS (lisinopril), and RAM (ramipril) as references (Table- 2).[24] Binding affinities and molecular interactions were assessed, as these are critical

for inhibitory efficacy. More negative binding energies indicate stronger protein-ligand affinity.[25,26] The inhibition constant (Ki) represents the compound concentration required to achieve half-maximal enzyme inhibition.[27] Generally, compounds with a Ki < 100 mM are considered potential inhibitors, while those with a Ki > 100 mM are classified as non-potent inhibitors.[28] In order to interact with ACE, compounds must bind key amino acid residues (Fig.-2). The compound must be a hydrogen bond (HB) acceptor to Lys511 and close to Gln281 and Tyr520. Otherwise, the HB acceptor group with His353 and/or His513 are also important, along with interactions with Ala356.[29] CPT had a binding energy of -6.58 kcal/mol and a Ki of 15.11 μM. It adhered to crucial binding constraints, forming HBs with Lys511, Gln281, and Tyr520, affirming its clinical efficacy as an ACE inhibitor. Other FDA-approved inhibitors, RAM and LIS, showed binding energies of -7.13 kcal/mol and -7.75 kcal/mol, respectively. RAM interacted with Lys511 and Asn277, while LIS formed an extensive HB network with Gln281, Ala354, and Lys511. Among the tested secondary metabolites, mol 17 showed the most promising compound, with a binding energy of -9.09 kcal/mol and a Ki of 215.73 nM. It formed key HBs with Lys511, His353, and His513, suggesting a strong inhibition profile due to the favourable binding conformation. Other notable compounds included mol 5 and mol 21. Mol 5 had a binding energy of -8.26 kcal/mol and a Ki of 877.88 nM, interacting with His353 and Asp453, Lys511, and Tyr520. Mol 21 showed a binding energy of -8.30 kcal/mol and a Ki of 827.48 nM, forming HBs with Gln281 and His353. In contrast, mol 3 and mol 28 showed moderate binding affinities (-6.79 kcal/mol and -6.15 kcal/mol, respectively), with fewer interactions. Mol 3 interacted with His513 and Tyr523, while mol 28 formed HBs with Gln281 and Asp453 but lacked significant interactions with Lys511, a vital residue for strong binding. This suggests that while these compounds may somewhat inhibit ACE, their overall efficacy could be limited due to suboptimal interactions with critical active site residues. Mol 19 exhibited unique binding characteristics. It showed a binding energy of -7.89 kcal/mol and a Ki of 1.66 μM, with notable interactions with Ala354 and His383 but not Lys511. These distinct binding characteristics suggest a potentially different inhibitory mechanism.

Table-2: Predicted Binding Energy (ΔG) and Inhibition Constant (Ki) of Kawista Secondary Metabolites and Reference ACE Inhibitor against ACE

No	Compound	Binding Energy (Kcal/mol)	Predicted *Ki*
1	Captopril	-6.58	15.11 μM
2	Ramipril	-7.13	5.94 μM
3	Lisinopril	-7.75	2.08 μM
4	Mol 2	-4.48	523.79 μM
5	Mol 3	-6.79	10.50 μM
6	Mol 4	-5.7	66.36 μM
7	Mol 5	-8.26	877.88 nM
8	Mol 6	-4.86	273.17 μM
9	Mol 7	-6.35	22.07 μM
10	Mol 8	-7.39	3.84 μM
11	Mol 11	-5.77	58.77 μM
12	Mol 16	-6.16	30.61 μM
13	Mol 17	-9.09	215.73 nM
14	Mol 18	-5.48	96.96 μM
15	Mol 19	-7.89	1.66 μM
16	Mol 20	-6.65	13.43 μM
17	Mol 21	-8.3	827.48 nM
18	Mol 22	-7.89	1.65 μM
19	Mol 25	-8.88	310.25 nM
20	Mol 28	-4.96	231.40 μM
21	Mol 29	-6.15	31.21 μM
22	Mol 30	-7.04	6.95 μM
23	Mol 31	-7.7	2.27 μM

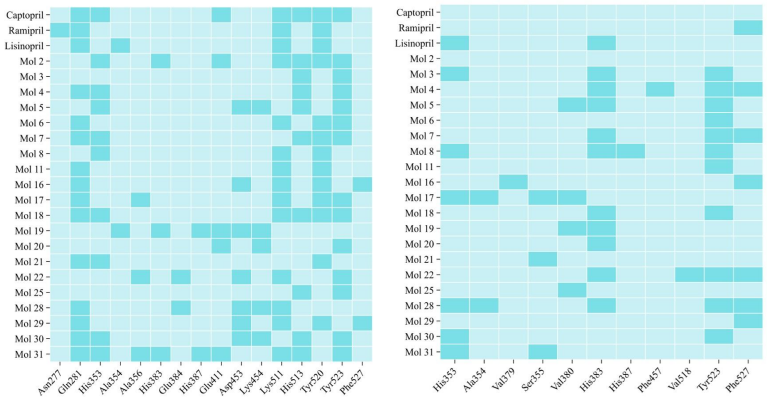

Fig.-2: Predicted Interactions between ACE and Selected Ligands Showing Hydrogen Bonding (left) and Hydrophobic Interactions (right); Dark Blue Indicates Interaction, While Light Blue Indicates no Interaction

Overall, molecular docking revealed varied binding affinities and interaction profiles. Mol 17 (limodissimin A) (Fig.-3) stood out as the most promising candidate. Interactions with Lys511 and HB acceptor group interactions with His353/His513 were crucial for determining the inhibitory potential. These insights support the potential of these compounds as ACE inhibitors and warrant further in vitro and in vivo studies. Importantly, the strong binding affinity and favourable interaction profile of mol 17. suggest that it may exhibit competitive inhibitory activity comparable to established ACE inhibitors. This finding contributes to the growing body of research on plant-derived ACE inhibitors, highlighting kawista as a promising natural source for antihypertensive drug discovery.

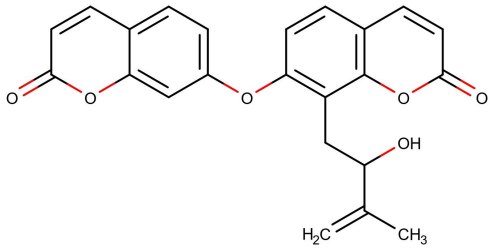

Fig.-3: Chemical Structure of Limodissimin A

Molecular Dynamics Simulations

RMSD analysis provided insights into protein-ligand stability and conformational shifts. Lower RMSD values indicate higher structural stability.[30,31] Fig.-4A shows the MD simulation for ACE and complex (ACE and limodissimin A) over 100 ns. The RMSDBb indicates the movement of atoms on the ACE protein's backbone, while RMSDAll includes all atoms.[32] ACE without ligand showed higher RMSD early in the simulation, indicating conformational shifts.[33]

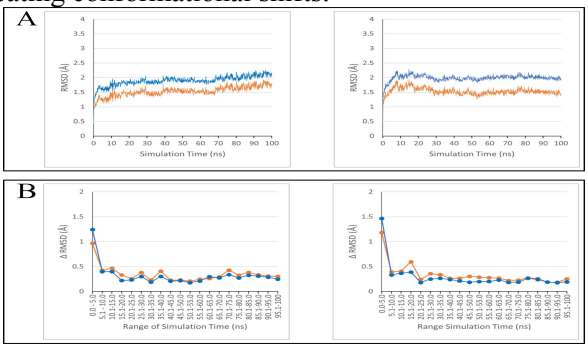

Fig.-4: (a) RMSD Values and (b) their Average Values Calculated Every 5 ns. Orange Represents RMSDBb, and Blue Represents RMSDAll. In Both Panels, the Left Shows the ACE Enzyme Without Ligand, while the Right Shows the ACE–limodissimin A Complex

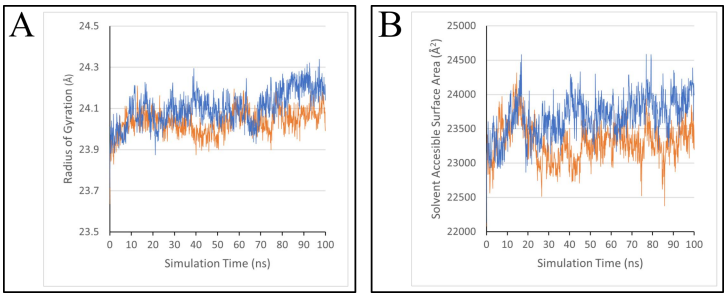

Fig.-5: (a) Rg and (b) SASA of ACE (blue) and the ACE–limodissimin A Complex (orange)

The simulation phases include initial adjustment (0–10 ns), transition (10–20 ns), and production (after 20 ns). RMSD values < 2 Å suggest a stable conformation. During production, the complex's RMSD maintained values under this threshold, while ACE's RMSD exceeded 2 Å after 70 ns, highlighting greater stability in the ligand-bound form. This finding has significant implications for further research and applications, suggesting that limodissimin A could stabilise protein conformations. Furthermore, ΔRMSD values were calculated every 5 ns (Fig.-4B). The ΔRMSD analysis provides a perspective on the changes in RMSD dynamics from one-time interval to the next.[34] Stability is indicated by ΔRMSD < 2 Å in the last 5 ns of simulation.[11,35] The complex had lower ΔRMSD (ΔRMSDBb = 0.254 ns; ΔRMSDAll = 0.193 ns) than ACE (ΔRMSDBb = 0.304 ns; ΔRMSDAll = 0.247 ns). This result suggests that the presence of limodissimin A, with its consistently lower ΔRMSD values, significantly stabilises the protein's conformation. The radius of gyration Rg measures molecular compactness.[36] Lower Rg suggests greater stability and efficient biological interactions.[37] Initially, ACE's Rg is approximately 23.714 Å, while the complex's Rg is slightly lower at around 23.637 Å (Fig.-5A). By the final 5 ns, the complex's average Rg was 24.083 Å, slightly lower than ACE's 24.208 Å, indicating a more compact and stable structure. The SASA (solvent accessible surface area) revealed the extent of solvent exposure.[38] At 0 ns, the complex's SASA was 22,077.41 Å², and ACE's SASA was 22,132.218 Å². The complex showed minor fluctuations, peaking at 13 and 15 ns, reaching 24,078.271 Å² and 24,041.145 Å², respectively (Fig.-5B), likely due to conformational flexibility. ACE displays greater variability in SASA, particularly between 20-30 ns, peaking at 24,895 Å² around 25 ns, indicating more structural rearrangement. ACE consistently showed higher SASA than the complex, suggesting that ligand binding stabilises the protein and reduces solvent exposure. These findings reinforce the docking results by demonstrating that limodissimin A not only binds strongly to ACE but also maintains structural stability under dynamic conditions. This combined evidence strengthens its potential as a candidate for further development as a natural ACE inhibitor and supports its relevance in the search for safer and more accessible antihypertensive therapies.

CONCLUSION

Limodissimin A, a secondary metabolite of kawista, demonstrated favourable oral bioavailability, strong
Limodissimin A, a secondary metabolite of kawista, demonstrated favourable oral bioavailability, strong binding affinity toward ACE (−9.09 kcal/mol; Ki = 215.73 nM), and stable protein–ligand interactions based on molecular dynamics simulations. These findings indicate that limodissimin A is a promising candidate for ACE inhibition. Further experimental validation through in vitro and in vivo studies is recommended to confirm its therapeutic potential and support the development of safer and more accessible antihypertensive agents.

ACKNOWLEDGMENTS

We thank the Faculty of Health Sciences, University of Muhammadiyah Malang, for funding this research.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

The present work is related to *SDG-3: Good Health and Well-being*. 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:

E.J.Astuti https://orcid.org/0000-0001-8703-7006
M.A. Muchlisin https://orcid.org/0000-0002-0257-4089
D. Elvina https://orcid.org/0009-0002-4878-2286
A. Rafikayanti https://orcid.org/0009-0002-9404-4903

Cite this article as: E. J. Astuti *et al.*, *Rasayan J. Chem.*, 19(3), 1808-1815(2026), https://doi.org/10.31788/RJC.2026.1939669

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[RJC-9669/2026]