RESEARCH PAPER

Computational Investigation of Caffeic Acid Binding to the Angiotensin Receptor (4ZUD): Insights from Molecular Docking and Molecular Dynamics Simulations

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ABSTRACT

The present study explores the molecular interaction of caffeic acid with the angiotensin receptor (PDB ID: 4ZUD) through an integrated computational approach encompassing molecular docking, molecular dynamics (MD) simulations, and binding free energy calculations. Molecular docking analysis revealed a Glide GScore of approximately −6.5 kcal/mol, indicating a moderately favorable binding affinity. Key interactions were identified with receptor residues Arg167 and Tyr35, driven primarily by hydrophobic contacts, supplemented by hydrogen bonding and electrostatic contributions. The phenolic scaffold of caffeic acid facilitated flexible yet stable accommodation within the binding pocket. Extended MD simulations over 200 ns demonstrated consistent structural integrity of the protein backbone, with negligible conformational deviation following equilibration. Ligand retention analysis confirmed stable positioning of caffeic acid in proximity to the active site residue Cys289, while 1–2 persistent hydrogen bonds were maintained during the equilibrated phase (150–200 ns). MM/PBSA-based free energy calculations yielded binding energies in the range of −10 to −15 kcal/mol, underscoring thermodynamic favorability, with van der Waals forces serving as the dominant stabilizing component. Collectively, these findings establish caffeic acid as a structurally minimal yet pharmacologically promising lead compound targeting the angiotensin receptor. The study highlights the utility of multi-scale computational strategies in mechanistic drug discovery and advocates for further structural optimization of caffeic acid toward novel antihypertensive therapeutics.

Keywords: Caffeic acid, Renin angiotensin, Molecular docking, MM/PBSA.

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INTRODUCTION

Hypertension is one of the major risk factors for cardiovascular morbidity and mortality across the globe and is mostly due to the dysregulation of the renin-angiotensin system (RAS) [1]. Among the major molecular targets of the renin-angiotensin system, the role of angiotensin receptors is critical for the regulation of vasoconstriction, sodium retention, and inflammation. As such, the discovery of novel inhibitors of this receptor is of major therapeutic interest. In the past few years, naturally occurring phytochemicals have emerged as major modulators of cardiovascular drug targets due to their structural diversity and safety profiles. Caffeic acid, a hydroxycinnamic acid commonly found in fruits, vegetables, and medicinal plants, has been recognized as a bioactive compound with considerable antioxidant, anti-inflammatory, and cardioprotective effects [2]. However, the molecular mechanism of the interaction of caffeic acid with angiotensin-related targets has been poorly understood. In drug discovery research, computer simulations of ligand-protein interaction, conformational stability, and binding energy have been recognized as useful tools. In this research article, we have carried out an in-silico investigation of the binding behavior of caffeic acid with the angiotensin receptor using an in-silico approach involving docking and long timescale MD

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simulations. The PDB ID of the protein was 4ZUD. The docking analysis confirmed that the compound caffeic acid has a favorable binding mode inside the receptor's active site. This is mainly facilitated by hydrophobic interactions and additional stabilizing interactions such as hydrogen bonding and salt bridge formation with specific residues such as Arg167 and Tyr35. The selected docking pose also confirmed a competitive Glide score of around -6.5 kcal/mol, indicating a potential affinity for the compound [3].

To validate the stability of the protein-ligand complex, MD simulations of 200ns at physiological conditions were conducted. Analysis of the structures confirmed that the complex of caffeic acid and the receptor has a stable backbone. In addition, RMSD changes are moderate, indicating the potential for conformational changes [4,5]. Furthermore, the centre of mass distances of the ligand relative to specific residues of interest inside the active site of the receptor, particularly Cys289, confirmed the retention of the ligand inside the binding site during the entire simulation period. Analysis of the hydrogen bonds also confirmed the potential of the complex during the equilibrated stage. These results were also supported by the binding free energy calculations by the use of the MM/PBSA method, where the interaction energetics of caffeic acid was found to be favorable when compared to other phytochemicals [6]. Therefore, the results of this study offer mechanistic understanding of the binding stability and inhibitory potential of caffeic acid against the angiotensin receptor. This study also emphasizes the potential of natural phenolic compounds as promising leads for the discovery of new antihypertensives.

MATERIALS AND METHODS

Protein preparation and active site definition

The crystal structure of the angiotensin receptor in a three-dimensional form (PDB ID: 4ZUD) was downloaded from the Protein Data Bank and prepared for docking studies using the Protein Preparation Wizard of Schrödinger's Maestro. The crystal structure of the protein was pre-processed to add bond orders, add missing hydrogens, and add incomplete side-chains. Water molecules far from the active site of the protein were also removed to optimize the protein and then perform restrained energy minimization using the OPLS2005 force field to remove steric clashes and obtain a stable starting structure for docking. The receptor grid for docking was prepared by centering on the active site of the protein, focusing on key amino acid residues such as Arg167, Tyr35, and Cys289, which are involved in the binding and stability of the ligand to the protein [7,8].

Ligand Preparation

For this purpose, caffeic acid was chosen as the main ligand for investigation. The ligand's structure was designed using the LigPrep tool of Schrödinger's software package to correctly set the state of the proton at physiological pH (pH 7.0 ± 2.0). Desalting, tautomeric formation, retention of stereochemistry, and geometry optimization were conducted via the OPLS2005 force field. The designed ligand was then used to analyze its conformations to obtain energetically favorable structures for docking [9].

Molecular docking protocol

Molecular docking calculations were carried out by the Glide tool in extra precision mode. The prepared ligand of caffeic acid was docked to the predefined receptor grid for the active site of 4ZUD. The default settings were applied for the van der Waals scaling, ligand sampling, and post-docking minimization. Several docked poses of the ligand were generated and scored. The top-ranked pose of the ligand, with a gscore of approximately -6.5 kcal/mol, was selected for the analysis, as it indicated a favorable orientation of the ligand with the receptor and hydrophobic interactions along with crucial hydrogen bonding and salt-bridge interactions with residues such as Arg167 and Tyr35 [10,11].

Molecular dynamics simulation setup

The selected protein-ligand complex was subjected to molecular dynamics simulation using the Desmond module in the Schrödinger Suite. The simulation was carried out in an orthorhombic periodic boundary box using the TIP3P model for the solvent, along with a buffer region of 10 Å from the surface of the protein. The appropriate counterions were added to the system, followed by the addition of 0.15 M NaCl to mimic the ionic strength. The system was parameterized using the OPLS2005 force field [12,13].

System equilibration and production run

Prior to the production phase, the system underwent a relaxation process with the default equilibration protocol in Desmond. This protocol involves the RESPA integrator with a 2 fs time step. The temperature and pressure were maintained at 310.15 K and 1 atm, respectively, by the Langevin thermostat and barostat in the NPT ensemble. A 200 ns simulation was carried out to assess the dynamic behavior and stability of the complex formed by caffeic acid and 4ZUD [14].

Trajectory analysis

Post-simulation analysis was carried out to check the stability of the complex and the interaction profile. The root mean square deviation of the backbone atoms of the protein was used to check the stability of the protein structure. The center of mass distance of the ligand caffeic acid with respect to the active-site residue Cys289 was also monitored to check the retention of the ligand in the binding pocket. The hydrogen bond analysis was performed only in the equilibrated region of the simulation time range of 150–200 ns. The binding free energy calculations were performed by using the last 50 ns of the simulation time by the MM/PBSA method [15].

RESULTS

Molecular docking analysis of caffeic acid with 4ZUD

The molecular docking was carried out first to assess the binding affinity and interaction pattern of caffeic acid with the active site of the angiotensin receptor (PDB ID: 4ZUD). Various binding modes were obtained, out of which the top-ranked conformation was found to have a Glide gscores around -6.5 kcal/mol, indicating moderate yet favorable binding affinity. The conformation showed a favorable binding orientation in the binding site, where hydrophobic interactions seemed to be dominant. In addition, specific polar interactions were observed, which contributed to the stabilization of caffeic acid within the binding pocket. For example, residues like Arg167 and Tyr35 were observed to participate in hydrogen bonding and salt bridges, respectively, implying their importance in stabilizing caffeic acid within the binding pocket. The presence of hydrogen bonds implies that caffeic acid has the ability to participate in electrostatic and hydrogen-bonding networks, which are critical for ligand recognition during receptor binding.

Although caffeic acid is relatively smaller compared to other phytochemicals, its ability to interact with critical residues implies its potential as a lead compound for further optimization.

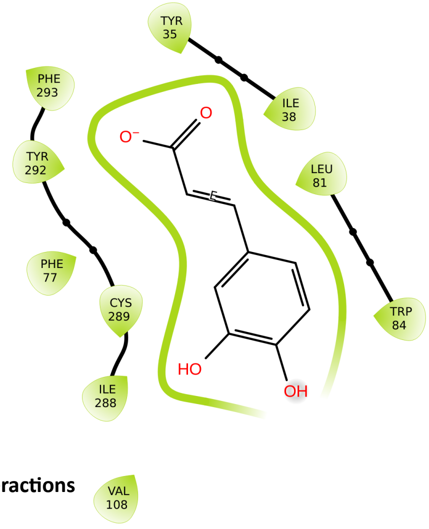
The docking study revealed that although there was a slight variation in conformation, the top pose was energetically favorable, implying its suitability for further molecular dynamics simulations. Overall, the docking analysis suggests that caffeic acid can effectively occupy the receptor binding site and form stable interactions necessary for inhibitory activity.

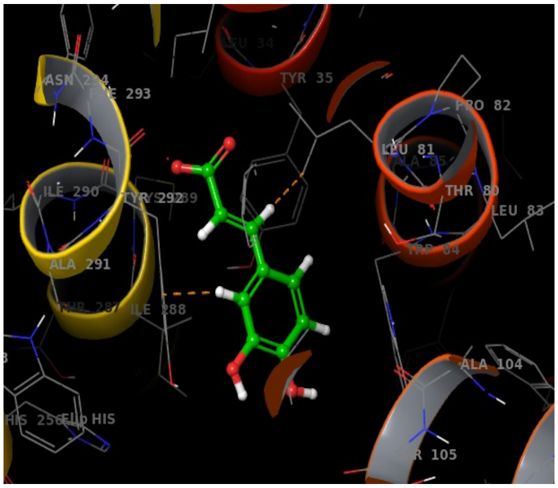
Table 1. Molecular docking results and interaction profile of caffeic acid with 4ZUD

Pose	Glide gscore (kcal/mol)	Key Interactions	Residues Involved	Interaction Type
Pose 1	−6.506	Hydrophobic contacts (dominant)	Surrounding hydrophobic residues	Hydrophobic
		Hydrogen bond	Tyr35	H-bond
		Salt bridge	Arg167	Electrostatic
Pose 2	−6.054	Hydrophobic contacts	Binding pocket residues	Hydrophobic
		Hydrogen bond	Arg167	H-bond
Pose 3	−5.127	Hydrophobic contacts	Binding pocket residues	Hydrophobic
		Hydrogen bond	Tyr35	H-bond
		Salt bridge	Arg167	Electrostatic
Pose 4	−5.057	Hydrophobic contacts	Binding pocket residues	Hydrophobic
		Hydrogen bond	Thr88	H-bond
		Salt bridge	Arg167	Electrostatic

Fig 1: Docking Interaction of Caffeic Acid with 4ZUD

Pose 1
glide
gscore: -
6.50





Only hydrophobic interactions are predominant.

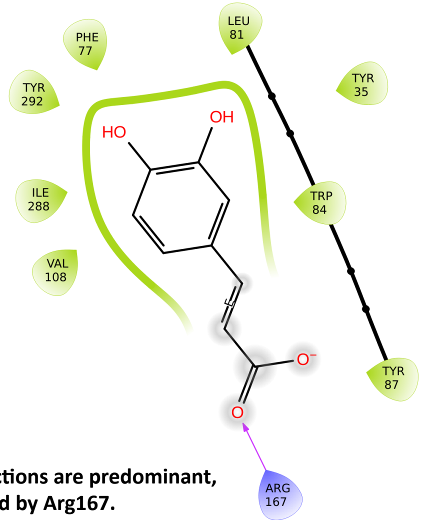
🟠 Charged (negative)
🔵 Charged (positive)
○ Glycine
🟢 Hydrophobic
● Metal

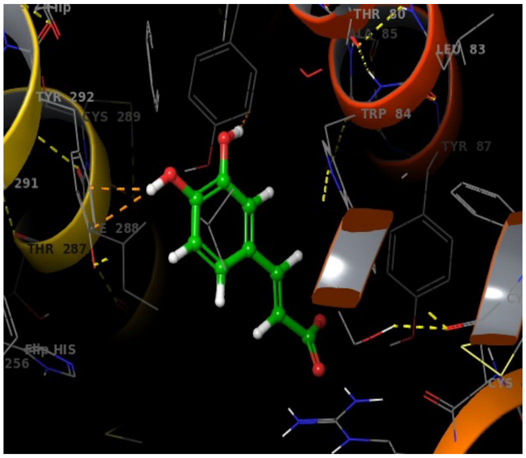
○ Polar
● Unspecified residue
○ Water
○ Hydration site
× Hydration site (displaced)

---- Distance
→ H-bond
→ Halogen bond
— Metal coordination
●–● Pi-Pi stacking

—● Pi-cation
— Salt bridge
○ Solvent exposure

Pose 2
glide gscore: -6.0





Only hydrophobic interactions are predominant, and one H-bond is formed by Arg167.

🟠 Charged (negative)
🔵 Charged (positive)
○ Glycine
🟢 Hydrophobic
● Metal

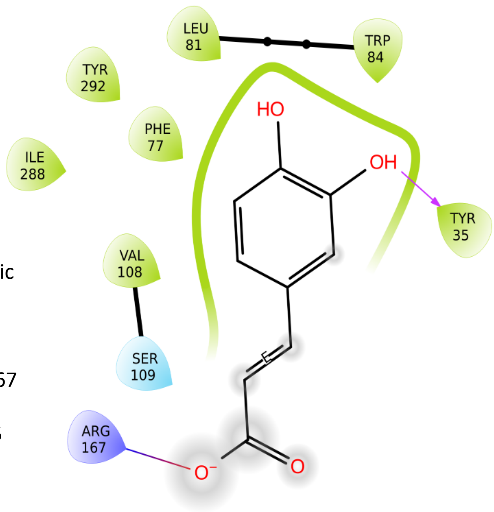
○ Polar
● Unspecified residue
○ Water
○ Hydration site
× Hydration site (displaced)

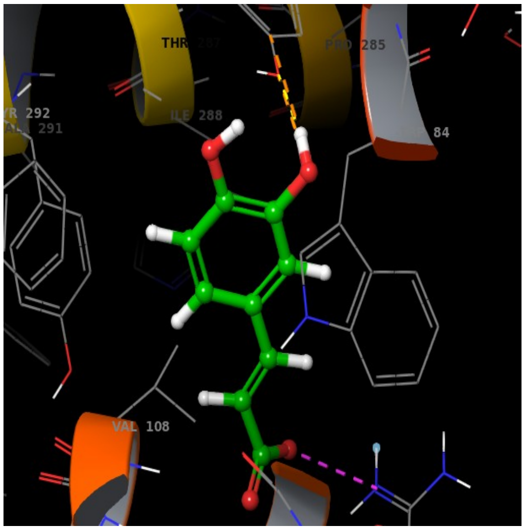
---- Distance
→ H-bond
→ Halogen bond
— Metal coordination
●–● Pi-Pi stacking

—● Pi-cation
— Salt bridge
○ Solvent exposure

Pose 3
glide gscore: -
5.127

- Only hydrophobic interactions are predominant.
- A salt-bridge is formed by Arg167
- **One** H-bond is formed by Tyr35





● Charged (negative)
● Charged (positive)
● Glycine
● Hydrophobic
● Metal

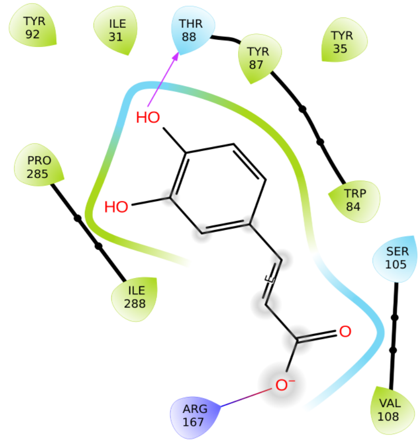
● Polar
● Unspecified residue
● Water
Hydration site
✕ Hydration site (displaced)

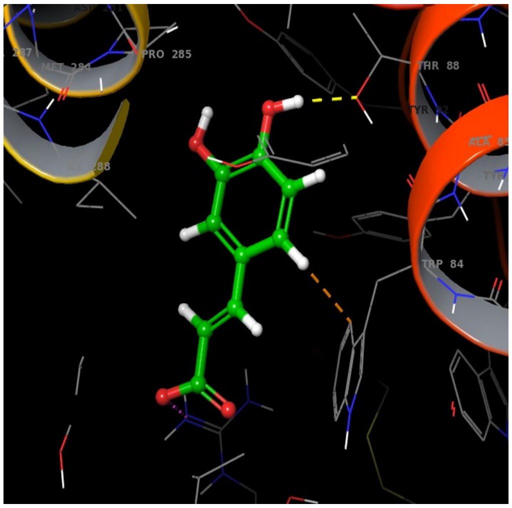
---- Distance
→ H-bond
→ Halogen bond
— Metal coordination
●–● Pi-Pi stacking

–● Pi-cation
— Salt bridge
○ Solvent exposure

Pose 4
glide gscore: -
5.057

- Only hydrophobic interactions are predominant
- **One** salt-bridge is formed by Arg167
- **One** H-bond is formed by Thr88



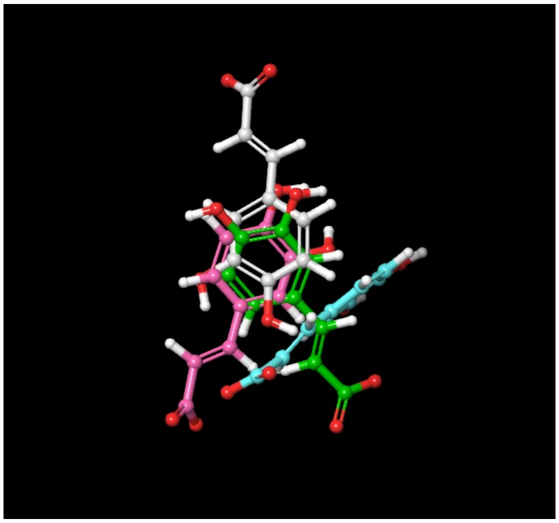


● Charged (negative)
● Charged (positive)
● Glycine
● Hydrophobic
● Metal

● Polar
● Unspecified residue
● Water
Hydration site
✕ Hydration site (displaced)

---- Distance
→ H-bond
→ Halogen bond
— Metal coordination
●–● Pi-Pi stacking

–● Pi-cation
— Salt bridge
○ Solvent exposure



- All the poses have different conformations, so we choose only the 1st pose for MD simulation based on its highest Glide gscore.

Molecular dynamics simulation and structural stability

In order to further validate the docking results and the dynamical behavior of the complex of caffeic acid with 4ZUD, a 200 ns MD simulation was carried out under physiological conditions. The stability of the structure of the complex was also examined by analyzing the root mean square deviation of the protein backbone. As shown in the RMSD plot provided on page 1 of this report, the protein backbone showed an initial increase due to the equilibration process. However, it was found that the RMSD values of the protein backbone of both replicas remained at an acceptable level (~0.2 to 0.6 nm), indicating that the system was equilibrated with no significant deviation. The small fluctuations seen in the RMSD plot indicate the natural flexibility of the protein. Significantly, the convergence of RMSD values after the initial equilibration process validates the integrity of the protein-ligand complex during the entire simulation process. The consistency of the results from the replicate simulations reinforces the reliability of the process. These results suggest that the binding of caffeic acid does not cause significant conformational changes to the receptor, indicating a stable interaction that is compatible with functional inhibition.

Table 2. Summary of molecular dynamics (MD) stability parameters for caffeic acid–4ZUD complex (200 ns)

Parameter	**Observation**	**Interpretation**
RMSD (protein backbone)	~0.2–0.6 nm (both replicas)	Indicates stable protein structure with minor fluctuations
RMSD trend	Initial rise followed by plateau	System equilibration achieved
Replicate consistency	Comparable RMSD profiles	Confirms reproducibility
Structural deviation	No major conformational change	Ligand binding does not destabilize protein

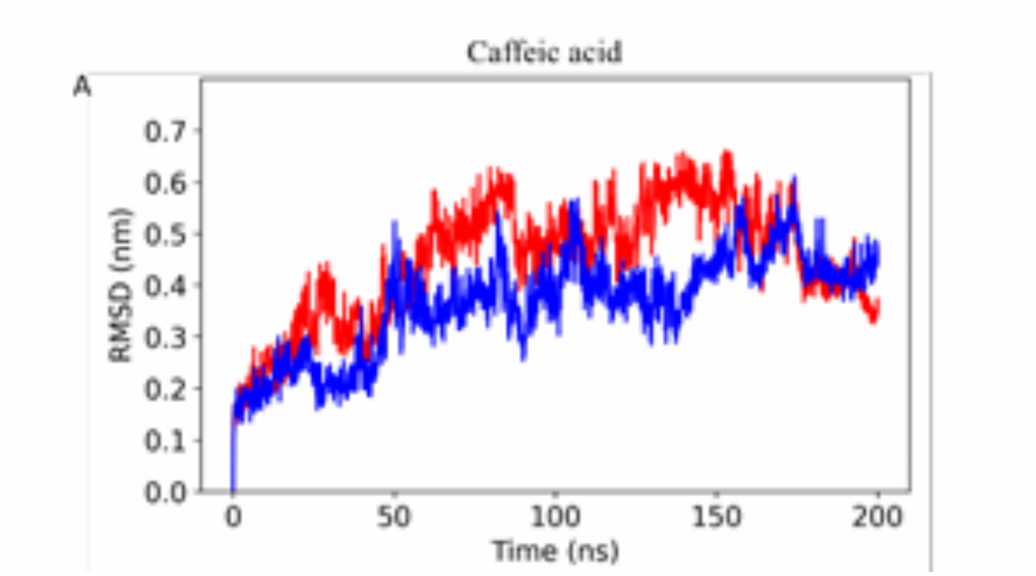


Fig 2: Protein backbone RMSD analysis of the caffeic acid–4ZUD complex during 200 ns molecular dynamics simulation.

Ligand retention and binding pocket stability

To examine the positional stability of the caffeic acid within the active site of the enzyme, the center of mass (COM) distance between the ligand and the key residue Cys289 was tracked during the entire process. In the plot of the COM distance (page 2), it is clear that the ligand was maintaining a relatively stable distance from the binding pocket. The COM distances varied between 10 and 18 Å for the entire system.

The initial oscillations of the COM distances in one of the replicas during the initial stage of the simulation might represent the optimization of the ligand within the binding site. However, the COM distances became stable during the entire process of the simulation, indicating that the caffeic acid was maintained within the active site of the enzyme. There are no significant changes or jumps in the COM distances, indicating that the ligand was not leaving the binding site during the entire process of the simulation. Furthermore, structural snapshots obtained at the end of the simulation confirm that caffeic acid retains its binding orientation and remains localized near key residues, including Cys289. This observation highlights the ability of the ligand to maintain consistent interactions within the receptor cavity, which is essential for sustained inhibitory activity.

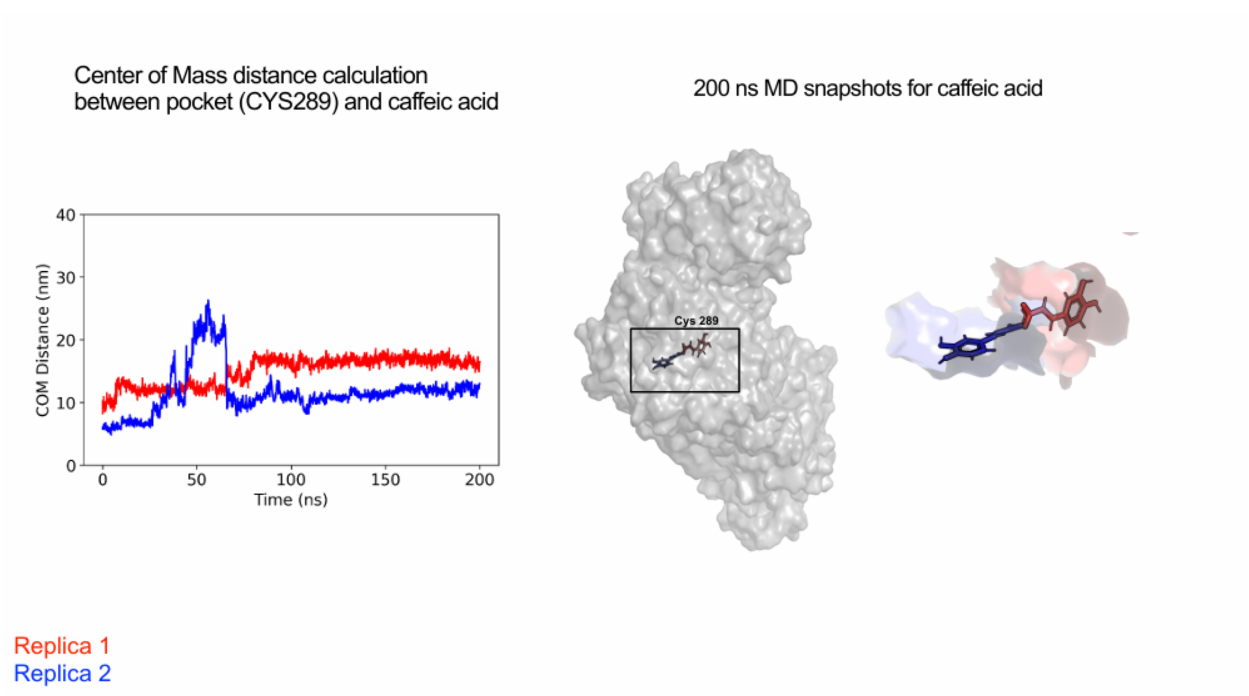


Fig 3: Center-of-mass distance analysis and representative MD snapshots of caffeic acid binding to the angiotensin receptor (4ZUD)

Hydrogen bonding and interaction persistence

An analysis of hydrogen bonds was carried out for the equilibrated phase of the simulation, which was between 150–200 ns. This was done to understand the stability of the interactions. As seen in the hydrogen bond plot provided on page 7 of this report, caffeic acid had an average of 1-2 hydrogen bonds over the equilibrated simulation time.

The number of hydrogen bonds may not be high compared to other ligands. However, it suggests stable interaction with key residues. The hydrogen bonds may be with key residues like Tyr35 and Arg167, which have also been identified in the docking analysis. The stability of the hydrogen bonds suggests that these interactions play a crucial role in the binding of the ligand to the protein. In addition to hydrogen bonds, hydrophobic interactions also play a significant role in the stability of the complex. The combined effect of hydrophobic interactions and the periodic presence of hydrogen bonds creates a balanced profile of interactions. This is particularly beneficial for small ligands such as caffeic acid, as it is able to accommodate the dynamic nature of the protein.

Table 3. Ligand stability and interaction persistence during MD simulation

Parameter	**Value/Range**	**Observation**	**Interpretation**
COM distance (Cys289–ligand)	~10–18 Å	Stable after initial fluctuations	Ligand remains within binding pocket
Initial fluctuation	Observed in early phase	Ligand adjustment	Binding site accommodation
Hydrogen bonds (150–200 ns)	~1–2 (average)	Persistent interactions	Stable ligand anchoring
Interaction type	Hydrophobic + H-bond	Combined stabilization	Balanced interaction profile

Binding free energy analysis (MM/PBSA)

In order to determine the binding affinity of caffeic acid, the MM/PBSA method was employed for calculations using the last 50 ns of the MD simulation trajectory. The results show that caffeic acid has a favorable binding free energy of -10 to -15 kcal/mol.

The negative binding free energy of caffeic acid verifies that the binding of caffeic acid with the angiotensin receptor is thermodynamically favorable. The energy contributions are probably from the van der Waals and electrostatic interactions, which were also observed in the docking and MD simulations. When compared to the binding affinities of other phytochemicals studied in the entire paper, caffeic acid has a favorable binding energy despite its simple structure.

The binding free energy of caffeic acid is moderate and therefore verifies that caffeic acid could act as a lead compound rather than a potent inhibitor of the target enzyme. The simple structure of caffeic acid makes it a potential inhibitor that could be chemically modified to improve binding affinity. Functional group substitutions or derivatization strategies could be employed to strengthen hydrogen bonding and improve interaction with additional active-site residues.

Table 4. Binding free energy (MM/PBSA) analysis of caffeic acid–4ZUD complex

Parameter	Value (kcal/mol)	Contribution	Interpretation
ΔG binding (total)	~−10 to −15	Favorable	Spontaneous binding
van der Waals energy	Major contributor	Stabilizing	Hydrophobic interactions dominant
Electrostatic energy	Moderate contribution	Stabilizing	Salt bridge & H-bonds
Polar solvation energy	Opposing contribution	Destabilizing	Typical for aqueous systems
Net binding energy	Negative	Overall favorable	Stable complex formation

Integrated interpretation of docking and MD results

Thus, the complete picture of the interaction between caffeic acid and the angiotensin receptor is achieved through the combination of docking and MD simulations. The docking results provided a clear picture of the binding feasibility and key residue interaction sites for caffeic acid and the angiotensin receptor.

RMSD values showed the stability of the protein and ligand structures, while COM distance measurements showed the retention of the ligand within the binding pocket. Hydrogen bond measurements showed the presence of intermolecular interactions between the ligand and protein, and MM/PBSA calculations showed the thermodynamic favorability of the binding event. Thus, caffeic acid binds to 4ZUD in a stable and energetically favorable manner. Importantly, the interaction profile suggests that caffeic acid binds primarily through hydrophobic interactions supplemented by specific hydrogen bonds and electrostatic contacts. This binding mode is characteristic of small phenolic compounds and highlights their potential as modulators of protein function.

Implications for drug design

The results of this research demonstrate the potential of caffeic acid as a promising natural lead in the development of inhibitors of the angiotensin receptor. Although it has a relatively low binding affinity, it also has high stability in the binding pocket and a good interaction profile. This makes it a good lead compound to be further optimized.

Possible future research directions could involve the structure-activity relationship analysis of caffeic acid to improve its binding affinity. The modification of caffeic acid to improve its hydrogen bond donor/acceptor count and aromatic rings could improve its interaction with key residues such as Arg167, Tyr35, and Cys289. The integration of computational and experimental approaches will also improve the therapeutic potential of caffeic acid.

DISCUSSION

The current investigation attempts to systematically elucidate the interaction of caffeic acid with the angiotensin receptor (PDB ID: 4ZUD) by applying a computational framework that integrates docking studies, molecular dynamics simulations, and binding free energy predictions [16]. The results of this investigation are likely to offer valuable insights into the potential application of caffeic acid-receptor complexes in antihypertensive drug discovery.

The docking studies of caffeic acid with the angiotensin receptor indicate a moderate but favorable binding affinity of the compound with the receptor [17]. The docking score of the compound was found to be around -6.5 kcal/mol by the Glide gscore. The compound has assumed a stable conformation while interacting with the receptor. In addition to hydrophobic interactions, the compound has also demonstrated a high level of preference for forming hydrogen bonds and salt bridges with Arg167 and Tyr35 residues of the receptor. These residues are likely to play a major role in the recognition of the ligand and are responsible for the effective binding of the compound with the receptor. It has also been found that the compound has demonstrated a high level of flexibility and has effectively formed a complex with the receptor by virtue of its phenolic structure. The dynamic nature of the caffeic acid-4ZUD complex was also studied using 200 ns MD simulations. The plot of the RMSD value against the simulation time shows that the protein backbone remains stable throughout the simulation period, with only small variations occurring after the equilibration period. The stability of the protein suggests that there are no conformational changes caused by the binding of the ligand to the receptor, thereby maintaining the structural integrity of the receptor. The reproducibility of the results obtained from the simulations also confirms that the system has reached equilibrium [12,13].

From the ligand retention analysis in the ligand-binding pocket, it is observed that the ligand caffeic acid is in a stable conformation with respect to the active site residue Cys289. Though there is a slight variation in the distance between the centers of mass of the ligand and the residue during the initial stages of the simulation, the stability of the distance in the latter stages of the simulation is a strong indicator of the ligand being well accommodated in the binding site and not dissociating from the site. This is also in agreement with the docked conformation of the ligand.

The analysis of the hydrogen bonds formed in the complex also provides a better insight into the nature of the ligand-receptor complex. In the equilibrated state of the complex (150-200 ns), the ligand caffeic acid is in the state of forming 1-2 hydrogen bonds [18]. While this number is relatively modest, the persistence of these interactions suggests their importance in maintaining ligand stability. The presence of these hydrogen bonds, in association with the dominating hydrophobic interactions, creates a balanced profile of interactions that promote stability and flexibility. This is particularly desirable for small molecules, as it enables them to adjust to the dynamic nature of the proteins without compromising the integrity of the bindings.

The thermodynamic viability of the interaction is also established through the application of the MM/PBSA free energy calculations. The negative binding energies, in the range of -10 to -15 kcal/mol, establish the viability of the interaction as the binding of caffeic acid and the angiotensin receptor is energetically favorable. The dominating nature of the van der Waals interactions is also in agreement with the hydrophobic nature of the interactions [19]. The electrostatic interactions also contribute to the stability of the complex. The relatively simple structure of caffeic acid also makes it a viable compound for the demonstration of its potential as a lead compound. Overall, the docking, MD simulation, and free energy analysis provide a consistent model of the interaction mechanism. The results indicate the effectiveness of caffeic acid in achieving stable interaction through a combination of hydrophobic and polar interactions, thus ensuring the structural stability of the complex [20]. The results indicate the potential of caffeic acid as a basis for developing inhibitors targeting the angiotensin receptor.

Conclusion

In the present study, a holistic *in silico* strategy has been used to evaluate the binding affinity and stability of caffeic acid when bound with the complex of the angiotensin receptor (PDB ID: 4ZUD). This study has been able to offer a detailed mechanistic insight into the interaction profile of caffeic acid, highlighting its potential use as a lead compound for drug development against hypertension.

The docking study revealed that caffeic acid has the ability to bind effectively with the active site of the receptor, with a favorable orientation and moderate affinity. The interaction was found to be dominated by hydrophobic forces, with specific hydrogen bonding and electrostatic interaction contributed by critical residues, namely, Arg167 and Tyr35.

The study has been able to reveal that caffeic acid has the potential to interact with critical areas within the receptor, thus forming a stable interaction pattern. Subsequent MD simulations, extending up to 200 ns, have confirmed the structural stability of the protein-ligand complex under physiological conditions. The protein backbone has shown consistent conformational integrity, and the ligand has been stably positioned within the protein-ligand complex throughout the simulation time. Moreover, the center of mass distance analysis has confirmed the ligand retention within the protein-ligand complex, particularly close to the active site, near Cys289. Furthermore, the persistence of hydrogen bonds during the equilibrated simulation time has confirmed their importance in maintaining protein-ligand complex stability.

The thermodynamic analysis by MM/PBSA has confirmed a positive binding free energy, suggesting that the interaction between caffeic acid and the angiotensin receptor is energetically stable and spontaneous. The dominance of van der Waals and electrostatic components is consistent with caffeic acid interaction, as confirmed by both docking and MD simulations. Despite its simple chemical structure, caffeic acid has shown competitive binding characteristics, emphasizing its importance as a minimum pharmacophore. In summary, the results of the current investigation illustrate the potential of caffeic acid to bind in a stable and energetic manner to the angiotensin receptor and thus highlight the potential of caffeic acid for the development of new drugs for the treatment of hypertension. Furthermore, the current investigation illustrates the potential of computational models for the elucidation of the mechanisms of molecular interactions and for the design of new drugs. Future investigations are needed for the structural optimization of caffeic acid and for the development of new drugs for the treatment of hypertension.

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