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In silico molecular docking and ADMET analysis of the phytochemicals of *Kalanchoe pinnata* (Lam.) Pers. as potential modulators of the mineralocorticoid receptor against cardiovascular diseases

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Abstract

Cardiovascular diseases represent a leading global health challenge, with a pronounced impact in low and middle-income countries. The mineralocorticoid receptor (MR), a key transcription factor in cardiovascular disorders, has been linked to hypertension, heart failure, and myocardial infarction. This study aims to investigate the potential of the phytochemicals in Kalanchoe pinnata (Lam.). Pers., a plant known for its traditional medicinal uses, in modulating MR activity through in silico approaches. Twenty phytochemicals belonging to different classes of organic molecules from the plant were subjected to computational screening to assess their interaction with the MR (PDB ID: 5L7E). MR was treated as a flexible receptor, and molecular docking was performed in a solvated environment. The molecule astragalin among the test molecules showed a promising binding score of -9.209 kcal/mol, which is comparable to the native ligand's score of -9.619 kcal/mol. ADMET predictions, including toxicity classification, revealed that most of the compounds demonstrated favorable gastrointestinal absorption and varying degrees of blood-brain barrier permeability. Toxicity evaluations revealed that several compounds exhibited moderate to low toxicity, with both astragalin and patuletin classified as Class 5, indicating a relatively higher level of safety compared to other phytochemicals, and a class comparable to the native compound (Class 6). These findings suggested that phytochemicals of K. pinnata hold potential for further investigation as modulators of MR activity, with implications for drug development in cardiovascular diseases.

Keywords: **Flexible molecular docking, computational approach, desolvation, docking score, pharmacokinetics, drug-likeness** .

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1 Introduction

Cardiovascular (CV) disease refers to a group of conditions that affect the heart and blood vessels. This includes hypertension, heart attack, stroke, heart failure, and other heart disorders [1]. CV disease is the leading cause of death worldwide, disproportionately affecting low- and middle-income countries more severely than high-income countries [2, 3]. The mineralocorticoid receptor (MR) is a transcription factor belonging to the steroid receptor family. Activation of the mineralocorticoid receptor is associated with various CV system disorders, such as hypertension, heart failure, and myocardial infarction [4, 5]. The increase in MR expression in the heart and blood vessels with age contributes to the higher incidence of CV diseases in the elderly [6, 7]. Enalapril and metoprolol are frequently prescribed for the treatment of CV conditions like hypertension and heart failure. Despite their effectiveness, these drugs may cause side effects, including dizziness, headaches, weakness, a drastic decrease in white blood cell count, proteinuria, and severe allergic reactions. To address these issues, this study focuses on exploring plant-based compounds as potential alternatives [8, 9]. Medicinal plants are recognized for containing compounds that may be valuable in treating diseases or in drug development [10, 11]. *Kalanchoe pinnata* (Lam.) Pers., a succulent herb, has long been utilized in traditional medicine to treat heart conditions, kidney stones, and cancer [12, 13]. They are used in folk medicine to relieve stomach pain and to treat gastritis, diarrhea, dysmenorrhea, liver disorders, fever, female infertility, genitourinary infections, snake and scorpion bites, leprosy, cough, asthma, kidney stones, arthritis, CV diseases, and general tiredness [14]. The plant extract exhibits antihypertensive activity as reported by various authors [15, 16], and forms the premise for this work.

Discovering new leads for a well-known target is a pivotal phase in drug development. Two primary approaches are employed: experimental high-throughput screening to sift through extensive compound libraries for potential leads, and computational methods that leverage structural data of the protein binding site [17]. To reduce the cost and time associated with extensive *in vitro* and *in vivo* experiments for identifying potential compounds in drug discovery and development, the use of *in silico* approaches is on the rise [18–20]. This technique employs a docking server to identify novel ligands for receptors with known structures, facilitating the screening of multi-compound databases for molecules that fit a receptor's binding site, thus eliminating the initial need for wet lab experiments [21–23]. This study involves an *in silico* screening of compounds from *K. pinnata* to assess their potential to modulate the MR protein and for molecular-level understanding of the relevant pathways associated with the modulation.

2 Methodology

2.1 Ligand Search

Twenty phytochemicals of *K. pinnata* were identified from the literature (Google Scholar, ResearchGate, PubMed, ScienceDirect) and are presented in Table 1 along with their PubChem CID. The compounds' structured data files (SDF) were downloaded from the PubChem database [23].

2.2 Protein Target Search

Probable targets were identified using the SuperPred web server (https://prediction.charite.de/) [24]. It is used for predicting the potential target proteins for a given set of ligands. A percentage bar indicates the probability of the ligand binding to the protein. This probability is based on structural similarity, binding affinity, and other computational predictions. The protein target with the highest probability, which was commonly found among all the ligands, was chosen. Other factors considered during this process included ensuring the protein resolution was below 2 Å, no mutations were present, and a native ligand was present. Eventually, a mineralocorticoid receptor target (PDB ID: 5L7E) with a resolution of 1.86 Å was chosen with a native ligand (6Q0). The structural data of the protein was retrieved from the RCSB protein bank (https://www.rcsb.org/) in PDB format..

2.3 Ligand Optimization

The native ligand (6Q0) was optimized before molecular docking by the use of the Avogadro program [25]. It is an advanced software for editing and visualizing molecules, used in computational chemistry, molecular modeling, and bioinformatics for optimizing molecular geometries [26]. The universal force field (UFF) was utilized to optimize the molecular geometries of the compounds, the conjugate gradient method was employed, and energy convergence was adjusted to 10^{-8} units to reduce their structural complexities [27, 28]. Alongside the native ligand, the same optimization process was applied to all the 20 compounds. After the optimization, it was saved in PDB format for molecular docking calculations.

Table 1: List of phytomolecules with their PubChem CID and canonical SMILES present in *K. pinnata*.

Molecule	Molecule name	PubChem CID	Canonical SMILES
1	Triacontane	12535	CCCCCCCCCCCCCCCCCCCCCCCCCCCCCC
2	Taraxerol	92097	CC1(CCC2(CC=C3C4(CCC5C(C(CCC5(C4CCC3(C2C1)C)C)O)(C)C)C)C)C
3	Stigmasterol	5280794	CCC(C=CC(C)C1CCC2C1(CCC3C2CC=C4C3(CCC(C4)O)C)C)C(C)C
4	Pseudotaraxasterol	12305110	CC1C2C3CCC4C5(CCC(C(C5CCC4(C3(CCC2(CC=C1C)C)C)C)(C)C)O)C
5	Patuletin	5281678	COC1=C(C2=C(C=C1O)OC(=C(C2=O)O)C3=CC(=C(C=C3)O)O)O
6	Palmitic acid	985	CCCCCCCCCCCCCCCC(=O)O
7	Isofucosterol	5281326	CC=C(CCC(C)C1CCC2C1(CCC3C2CC=C4C3(CCC(C4)O)C)C)C(C)C
8	Hentriacontane	12410	CCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCC
9	Glutinol	9932254	CC1(CCC2(CCC3(C4CC=C5C(C4(CCC3(C2C1)C)C)CCC(C5(C)C)O)O)C)C)C
10	Friedelin	91472	CC1C(=O)CCC2C1(CCC3C2(CCC4(C3(CCC5(C4CC(CC5)(C)C)C)C)C)C)C
11	Epigallocatechin	72277	C1C(C(OC2=CC(=CC(=C21)O)O)C3=CC(=C(C(=C3)O)O)O)O)O
12	Clionasterol	457801	CCC(CCC(C)C1CCC2C1(CCC3C2CC=C4C3(CCC(C4)O)C)C)C(C)C
13	Clerosterol	5283638	CCC(CCC(C)C1CCC2C1(CCC3C2CC=C4C3(CCC(C4)O)C)C)C(=C)C
14	Cardenolides	53957771	CC12CCCCC1CCC3C2CCC4(C3CCC4C5=CC(=O)OC5)C
15	Campesterol	173183	CC(C)C(C)CCC(C)C1CCC2C1(CCC3C2CC=C4C3(CCC(C4)O)C)C
16	Astragalin	5282102	C1=CC(=CC=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)OC4C(C(C(C(O4)CO)O)O)O)O
17	Arachidic acid	10467	CCCCCCCCCCCCCCCCCCCC(=O)O
18	Bersaldegenin-3-acetate	21768173	CC(=O)OC1CC(C2(C3CCC4(C(CCC4(C3CCC2(C1)O)O)C5=COC(=O)C=C5)C)C=O)O
19	Behenic acid	8215	CCCCCCCCCCCCCCCCCCCCCCC(=O)O
20	Syringic acid	10742	COC1=CC(=CC(=C1O)OC)C(=O)O

2.4 Protein Structure Optimization

The PDB structure with PDB ID of 5L7E was opened in the PyMOL program. When the water molecules are removed from a protein, it is known as the holoprotein. After the native ligand is extracted, the resulting structure is called the apoprotein. The extra chain present in the target was removed, polar hydrogens were added, and it was subsequently saved in PDB format.

2.5 Molecular Docking Calculations

Ligand-protein docking is an optimization problem focused on predicting the position and pose of a ligand that achieves the lowest binding energy within the receptor's active site. Docking aids in predicting the favorable binding geometries of a small molecule within a target protein's binding site and estimating the docking score of the resulting complex [29]. For the docking purpose, a web-based tool known as the DockThor (rigid receptor approach) (https://www.dockthor.lncc.br/) [30] was used. For this, the apo form of the protein, native ligand, and the test compounds were utilized in PDB form. Initially, to validate the molecular docking protocol, the approach used by Adhikari Subin and Shrestha (2024) was followed. The apoprotein and native ligand were uploaded to the server, and the following parameters were applied: grid center (x: 9, y: 14, z: 11), grid size (x: 16, y: 16, z: 16), discretization: 0.17, number of evaluations: 1,000,000, population size: 750, and number of runs: 24 [31]. Subsequently, the test compounds were docked using the same parameters as those for the native ligand. The docking score measures the strength of the interaction between the target and the molecule. It reflects the free energy change upon binding on a comparative basis, with more negative values indicating stronger interactions [30, 32, 33].

2.6 Protocol Validation via RMSD Calculation

Root mean square deviation (RMSD) measures the average distance between atoms in a predicted model and a reference structure, assessing how well the predicted model aligns with the experimental or reference structure. Lower RMSD values indicate a better fit, reflecting a more accurate prediction of the ligand's binding mode to the target protein [34]. An RMSD value below 2.0 Å [35] is widely accepted as the benchmark for distinguishing between successful and unsuccessful reproductions of a known binding mode [29, 36]. The heavy atom RMSD was calculated for the native ligand with the best binding affinity.

2.7 Protein-Ligand Interactions

PLIP server (https://plip-tool.biotec.tu-dresden.de/plip-web/plip/index) was used for visualizing three-dimensional representations of protein-ligand interactions [37].

2.8 ADMET Properties and Toxicity Class Identification

The *in silico* properties for absorption (gastrointestinal absorption and P-glycoprotein substrate/inhibitor status), distribution (blood-brain barrier permeability), metabolism (cytochrome P450 inhibition or substrate status), and excretion (clearance) were evaluated using the SwissADME server (https://www.swissdock.ch/). The toxicity class was determined through the ProTox 3.0 server (https://tox.charite.de/protox3/). It classifies compounds into six toxicity classes (1 to 6) based on their predicted lethal dose (LD_{50}) and potential toxic effects. Class 1 represents the most toxic compounds, while class 6 represents the least toxic.

3 Results and Discussion

3.1 Molecular Docking Protocol Validation

By superimposing the co-crystallized native ligand with the docked ligand, the heavy atom RMSD was calculated to be 1.79 Å, indicating that the docking protocol was reliable and predicted the ligand's

binding pose (Figure 1). The parameters were determined to be effective in capturing the presumed global minima of the protein-ligand adduct.

3.2 Binding Affinity and Strength of Interactions

The binding affinity of -9.691 kcal/mol found by the docking of the native ligand against the target suggested a strong interaction (Table 2). The lower (more negative) the binding energy, the more stable and stronger the binding between molecules [38]. Among the proposed compounds, astragalin (complex 1) exhibited the best binding affinity of -9.209 kcal/mol, which is the closest to that of the native ligand. Similarly, complex 2 (patuletin) demonstrated a binding affinity of -8.572 kcal/mol indicating slightly weaker interactions as compared to complex 1.

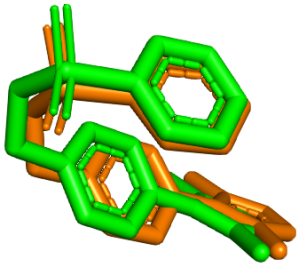
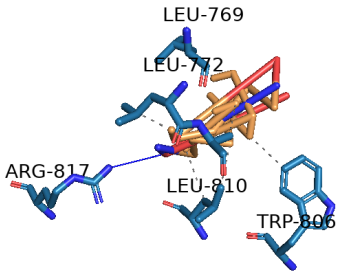


Figure 1: Superimposition of co-crystalized native ligand 6Q0 (brown) with docked ligand (green) (Heavy atom RMSD= 1.79 Å).

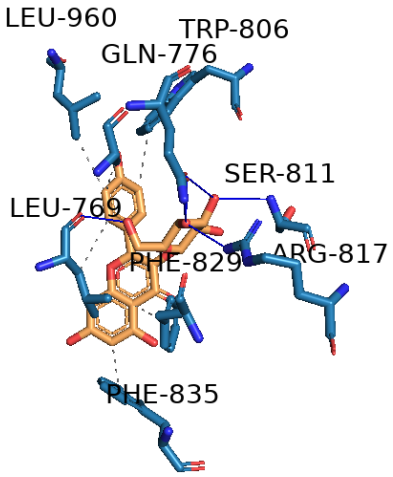
3.3 Present in the Protein-Ligand Complexes

Proteins interact with other small molecules to enhance or inhibit biological functions. In protein-ligand interactions, a few key residues play a pivotal role in recognizing counterparts and maintaining the affinity that binds the ligand to its receptor [39]. Identifying these key residues is essential for understanding protein function, analyzing molecular interactions, and guiding future experimental procedures [40].

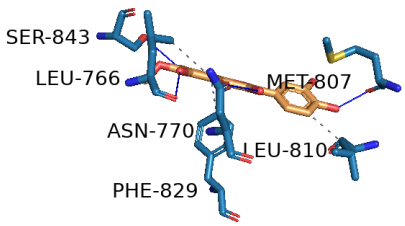
The interactions between different ligands and the target are illustrated in Figure 2. Table 2 shows that the native ligand formed hydrogen bonds with ARG817 at a distance of 3.29 Å. The distances between the ligand and the amino acids reveal the proximity of their interaction within the protein binding site. The shorter the distance, the stronger the interaction. In this context, the H-bonding interaction involving LEU769 in complex 1, with a distance of 1.71 Å, can be considered the strongest overall. Similarly, the interaction with MET807 in complex 2 is the strongest among all residues, with a distance of just 1.92 Å. The key amino acid residues (ARG817, TRP806, LEU769) involved in the interactions between astragalin (complex 1) and the target protein are nearly identical to those observed in the interaction between the native ligand and the protein. This suggests that the ligand binds at the catalytic site of the protein and is therefore capable of modulating it.



(Native)



(1)



(2)

Figure 2: 3D interactive representations of the key interactions of the ligand with active site residues in protein-ligand complex (native, 1 (astragalin), and 2 (patuletin)).

Table 2: Selected ligands, docking score, and types of interactions present in the adducts.

Interactions	Active residues in the adducts (distance in Å)		
	5282102-MR (complex 1)	5281678-MR (complex 2)	6Q0-MR
Hydrogen-bond	LEU769 (1.71), GLN776 (2.61), ARG817 (2.41)	LEU766 (3.02), ASN770 (2.41), MET807 (1.92), SER843 (2.35)	ARG817 (3.29)
Hydrophobic	LEU769 (3.89), ALA773 (2.90), TRP806 (3.51), PHE829 (3.73), PHE835 (3.25), LEU960 (3.64)	LEU766 (3.81), LEU810 (3.13), PHE829 (3.29)	LEU769 (3.62), LEU772 (3.59), ALA773 (3.76), TRP806 (3.52), LEU810 (3.71)
Docking score (kcal/mol)	-9.209	-8.572	-9.619

Note: MR= Mineralocorticoid receptor (target)

3.4 ADMET Analysis

The ADMET data via the SwissADME server and its analysis provided key insights into the absorption properties of the molecules. Molecules (triacontane and hentriacontane) were found to be insoluble with low gastrointestinal (GI) absorption. Their high lipophilicity (logP of 11.95 and 12.34, respectively) poses formulation and absorption challenges. In contrast, palmitic acid displayed high GI absorption, along with moderate solubility and permeability across the blood-brain barrier (BBB), making it a promising candidate. Bersaldegenin-3-acetate, while soluble and showing high GI absorption, was not BBB permeant and had moderate lipophilicity (logP of 2.08). Most of the molecules adhered to Lipinski's Rule of Five, except astragalin, which had a high topological polar surface area (TPSA) of 190.28 Å² and a low logP value of -0.24, making it unable to permeate the GI tract and, therefore, unlikely to enter the bloodstream [41] (Table 3). The low gastrointestinal absorption of Astragalin could potentially be improved through nanoparticle delivery, glycoside hydrolysis, or other formulation strategies such as lipid-based carriers and prodrug approaches.

Palmitic acid and cardenolide were the only compounds identified as BBB permeant, indicating their ability to cross the BBB and potentially target central nervous system (CNS) disorders. However, the BOILED-Egg model, based on TPSA and logP values, revealed that 7 out of the 20 molecules did not fall within the specified range for BBB permeation or high gastrointestinal absorption (Supplementary Figure 1). This limitation suggested that these molecules may not be as effective as orally administered or CNS-targeting compounds [42].

Of the 20 molecules analyzed, 12 did not inhibit any of the major enzymes (CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4) (Supplementary Table 1). This indicates that these molecules are less likely to disrupt the metabolism of other medications, thereby lowering the risk of drug-drug interactions [43]. This is particularly significant for patients on multiple drugs, as it suggests that these 12 molecules are unlikely to lead to adverse effects associated with the buildup of other drugs metabolized by these CYP enzymes [44].

Table 3: ADMET analysis of all 20 phytocompounds found in *K. pinnata*.

Molecule	Water solubility	GI absorption	BBB permeant	Pgp substrate	TPSA (Å²)	logP (WLOGP)	Lipinski Rule of 5
1	-	Low	No	Yes	0	11.95	Accepted
2	+	Low	No	No	20.23	8.17	Accepted
3	+	Low	No	No	20.23	7.8	Accepted
4	+	Low	No	No	20.23	8.02	Accepted
5					140.5		Accepted
	+++	Low	No	No	9	2	
6	++	High	Yes	No	37.3	5.55	Accepted
7	+	Low	No	No	20.23	7.94	Accepted
8	-	Low	No	Yes	0	12.34	Accepted
9	+	Low	No	No	20.23	8.17	Accepted
10	+	Low	No	No	17.07	8.46	Accepted
11					130.6		Accepted
	+++	High	No	No	1	0.93	
12	+	Low	No	No	20.23	8.02	Accepted
13	+	Low	No	No	20.23	7.94	Accepted
14	+	High	Yes	No	26.3	5.52	Accepted
15	+	Low	No	No	20.23	7.63	Accepted
16					190.2		Rejected
	+++	Low	No	No	8	-0.24	
17	+	Low	No	No	37.3	7.11	Accepted
18					134.2		Accepted
	+++	High	No	Yes	7	2.08	
19	+	Low	No	No	37.3	7.89	Accepted
20	+++	High	No	No	75.99	1.11	Accepted
Native (6Q0)	++	High	No	No	80.58	4.37	Accepted

Note: Water solubility is indicated as: insoluble (-), poorly soluble (+), moderately soluble (++), and highly soluble (+++). And rejection in the table indicates the violation of 2 rules of Lipinki.

The excretion properties of the phytocompounds were evaluated based on their clearance rates (mL/min/kg), revealing significant differences among the molecules. Astragalin demonstrated a low clearance rate of 3.126 mL/min/kg, suggesting that it remains in the body for a longer period before being eliminated. In contrast, pseudotaraxasterol and campesterol exhibited higher clearance rates of 19.75 mL/min/kg and 16.512 mL/min/kg, respectively (Supplementary Table 2). This indicates that they are rapidly cleared from the body, reducing the risk of accumulation and potential toxicity. Efficient excretion minimizes the chances of toxic buildup or prolonged exposure, making these molecules less likely to cause long-term toxicity compared to those with slower clearance rates.

Most of the molecules (11) were classified under Class 4 toxicity, indicating they are harmful and can lead to significant health effects at higher doses (890 mg/kg). However, they are less likely to be fatal than Classes 3, 2, and 1. Three molecules (triacontane, hentriacontane, and bersaldegenin-3-acetate) were classified as Class 3, which are toxic at moderate doses, while two were in Class 5, indicating they are less toxic but still harmful at very high doses. Three molecules (taraxerol, pseudotaraxasterol, and epigallocatechin) were determined to have Class 6 toxicity, suggesting they have low or negligible toxicity and are generally safe at typical exposure levels (7000 mg/kg). One molecule, identified as cardenolides, was categorized in Class 2, indicating high toxicity with potentially fatal effects at relatively low doses (34 mg/kg) (Supplementary Table 3). This suggests that even small

amounts could pose serious health risks, highlighting the need for caution in handling and potential therapeutic applications. For any practical use, such as in drug development or herbal preparations, rigorous dose optimization, careful monitoring, and safety assessments would be essential to prevent toxic effects. Additionally, formulation strategies or structural modifications may be required to mitigate toxicity while preserving any beneficial biological activity. Astragalin, although inactive across specific toxicity endpoints such as carcinogenicity, immunotoxicity, mutagenicity, and cytotoxicity, was classified in a safe toxicity class (Class 5). It demonstrated favorable outcomes in molecular docking studies, justifying further exploration.

Note: Water solubility is indicated as: insoluble (-), poorly soluble (+), moderately soluble (++), and highly soluble (+++). And rejection in the table indicates the violation of 2 rules of Lipinki.

The ADMET properties of several reference drugs (enalapril, metoprolol, ramipril, and digoxin) commonly used in the management of CV diseases are shown in Supplementary Table 4. With the highest TPSA (203.06 $Å^2$), digoxin may struggle to cross cell membranes, leading to its lower GI absorption and poor BBB permeability. All the drugs, except digoxin, showed high GI absorption, suggesting they are effectively absorbed orally. Despite digoxin being classified as Class 1 in toxicity, it is still used for the intervention of CV diseases. The ligand we studied, astragalin, is classified as Class 5 in toxicity and has good solubility and BBB permeability.

The phytochemicals astragalin and patuletin from *K. pinnata* demonstrated significant binding affinity to the mineralocorticoid receptor in molecular docking studies, suggesting their potential as modulators. Furthermore, their ADMET profiles indicate favorable solubility, good GI absorption, and BBB permeability, along with lower toxicity levels, making them promising candidates for CV drug development.

4 Conclusion

The results of this study underscore the potential of *Kalanchoe pinnata* phytochemicals as modulators of the mineralocorticoid receptor, with significant implications for CV disease management. The molecular docking analysis revealed that the phytochemical astragalin exhibited strong binding affinities close to the native ligand, suggesting its potential effectiveness in modulating MR activity. Furthermore, the ADMET analysis indicated that most of the studied compounds demonstrated favorable pharmacokinetic properties, including good gastrointestinal absorption, toxicity endpoints, and acceptable toxicity levels, with several compounds falling within safe toxicity classes. Notably, astragalin stands as a particularly promising candidate, exhibiting a strong binding affinity and low toxicity, making it a viable candidate for further investigation. These findings provide a formidable foundation for *in vitro* and *in vivo* studies to explore the possibilities of the therapeutic potential of *K. pinnata* phytochemicals in CV disease management.

Ethical approval

The research conducted is not related to either human or animal use.

Conflict of interest

The authors declare no conflict of interest.

References

[1] O. Gaidai, Y. Cao, and S. Loginov. Global cardiovascular diseases death rate prediction. *Current Problems in Cardiology*, 48(5):101622, May 2023.

[2] S. Bhattarai et al. Cardiovascular disease trends in nepal – an analysis of global burden of disease data 2017. *IJC Heart & Vasculature*, 30:100602, October 2020.

[3] B. Huang, C. Huang, L. Zhu, L. Xie, Y. Wang, and N. Zhu. Exploring the pharmacological mechanisms of tripterygium wilfordii hook f against cardiovascular disease using network pharmacology and molecular docking. *BioMed Research International*, 2021:1–11, August 2021.

[4] G. M. Kuster et al. Mineralocorticoid receptor inhibition ameliorates the transition to myocardial failure and decreases oxidative stress and inflammation in mice with chronic pressure overload. *Circulation*, 111(4):420–427, 2005.

[5] M. Buonafine, B. Bonnard, and F. Jaisser. Mineralocorticoid receptor and cardiovascular disease. *American Journal of Hypertension*, 31(11):1165–1174, 2018.

[6] A. W. Krug et al. Elevated mineralocorticoid receptor activity in aged rat vascular smooth muscle cells promotes a proinflammatory phenotype via erk1/2 mapk and egfr-dependent pathway. *Hypertension*, 55(6):1476–1483, 2010.

[7] I. Z. Jaffe and M. E. Mendelsohn. Angiotensin ii and aldosterone regulate gene transcription via functional mineralocortocoid receptors in human coronary artery smooth muscle cells. *Circulation Research*, 96(6):643–650, 2005.

[8] F. Moncloa, J. A. Sromovsky, J. F. Walker, and R. O. Davies. Enalapril in hypertension and congestive heart failure. *Drugs*, 30(Suppl 1):82–89, 1985.

[9] P. Wang, L. Wang, Z. Liu, and J. Feng. Safety and efficacy of enalapril combined with metoprolol in patients of hypertension complicated with coronary heart disease: A randomised clinical trial. *Journal of Clinical and Diagnostic Research*, pages 15–20, 2022.

[10] R. L. S. Shrestha, B. Maharjan, T. Shrestha, B. P. Marasini, and J. Adhikari Subin. Geometrical and thermodynamic stability of govaniadine scaffold adducts with dopamine receptor d1. *Results in Chemistry*, 7:101363, January 2024.

[11] S. Alam et al. Antidiabetic phytochemicals from medicinal plants: Prospective candidates for new drug discovery and development. *Frontiers in Endocrinology*, 13, 2022.

[12] M. E. Hernández-Caballero, J. A. Sierra-Ramírez, R. Villalobos-Valencia, and E. Seseña-Méndez. Potential of kalanchoe pinnata as a cancer treatment adjuvant and an epigenetic regulator. *Molecules*, 27(19):6425, September 2022.

[13] R. Rahman, J. N. Al-sabahi, A. Ghaffar, F. Nadeem, and A. Umar. Phytochemical, morphological, botanical, and pharmacological aspects of a medicinal plant: Kalanchoe pinnata – a review article. *International Journal of Chemical and Biochemical Sciences*, 16:5–10, 2019.

[14] O. S. M. Bopda et al. Antihypertensive activities of the aqueous extract of kalanchoe pinnata (crassulaceae) in high salt-loaded rats. *Journal of Ethnopharmacology*, 153(2):400–407, 2014.

[15] P. B. Rajsekhar, R. S. Arvind Bharani, M. Ramachandran, K. Jini Angel, and S. P. V. Rajsekhar. The 'wonder plant' kalanchoe pinnata (linn.) pers.: A review. *Journal of Applied Pharmaceutical Science*, 6(3):151–158, 2016.

[16] M. B. OS et al. Cardioprotective effects of kalanchoe pinnata aqueous and ethanolic extracts in wistar rat. *Annals of Hypertension*, 1(2):1–6, 2019.

[17] H. Gohlke, M. Hendlich, and G. Klebe. Knowledge-based scoring function to predict protein-ligand interactions. *Journal of Molecular Biology*, 295(2):337–356, 2000.

[18] B. Shaker, S. Ahmad, J. Lee, C. Jung, and D. Na. In silico methods and tools for drug discovery. *Computers in Biology and Medicine*, 137:104851, October 2021.

[19] V. S. Rao and K. Srinivas. Modern drug discovery process: An in silico approach. *Journal of Bioinformatics and Sequence Analysis*, 2(June):89–94, 2011. Available online: http://www.academicjournals.org/JBSA.

[20] R. Shrestha et al. Selected phytochemicals as potent acetylcholinesterase inhibitors: An in silico prediction. *Journal of the Serbian Chemical Society*, pages 1–14, 2024.

[21] P. Burkhard, U. Hommel, M. Sanner, and M. D. Walkinshaw. The discovery of steroids and other novel fkbp inhibitors using a molecular docking program. *Journal of Molecular Biology*, 287(5):853–858, 1999.

[22] S. Gupta et al. Identification of potential natural inhibitors of sars-cov2 main protease by molecular docking and simulation studies. *Journal of Biomolecular Structure and Dynamics*, 39(12):4334–4345, 2021.

[23] S. Kim et al. Pubchem 2023 update. *Nucleic Acids Research*, 51:1373–1380, 2023.

[24] J. Nickel et al. Superpred: Update on drug classification and target prediction. *Nucleic Acids Research*, 42(W1):26–31, 2014.

[25] M. D. Hanwell, D. E. Curtis, D. C. Lonie, T. Vandermeersch, E. Zurek, and G. R. Hutchison. Avogadro: An advanced semantic chemical editor, visualization, and analysis platform. *Journal of Cheminformatics*, 4(17), 2012.

[26] B. Rayan and A. Rayan. Avogadro program for chemistry education: To what extent can molecular visualization and three-dimensional simulations enhance meaningful chemistry learning? *World Journal of Chemical Education*, 5(4):136–141, 2017.

[27] E. Y. Salifu, J. Abugri, I. A. Rashid, F. Osei, and J. A. Ayariga. In silico identification of potential inhibitors of acyl carrier protein reductase and acetyl coa carboxylase of plasmodium falciparum in antimalarial therapy. *Frontiers in Drug Discovery*, 3, 2023.

[28] İ. H. Ciğerci et al. Cyto-genotoxic and behavioral effects of flubendiamide in allium cepa root cells, drosophila melanogaster and molecular docking studies. *International Journal of Molecular Sciences*, 24(2), 2023.

[29] D. Yusuf, A. M. Davis, G. J. Kleywegt, and S. Schmitt. An alternative method for the evaluation of docking performance: Rsr vs rmsd. *Journal of Chemical Information and Modeling*, 48(7):1411–1422, 2008.

[30] I. A. Guedes et al. Dockthor-vs: A free platform for receptor-ligand virtual screening. *Journal of Molecular Biology*, page 168548, March 2024.

[31] J. Adhikari Subin and R. L. S. Shrestha. Computational assessment of the phytochemicals of panax ginseng c.a. meyer against dopamine receptor d1 for early huntington's disease prophylactics. *Cell Biochemistry and Biophysics*, July 2024.

[32] M. K. Gilson and H.-X. Zhou. Calculation of protein-ligand binding affinities. *Annual Review of Biophysics and Biomolecular Structure*, 36(1):21–42, 2007.

[33] M. Poudel et al. Exploration of antioxidant, antibacterial, and alpha-glucosidase inhibition potential of cirsium verutum (d. don) spreng extracts: In vitro and in silico approach. *Asian Journal of Applied Chemistry Research*, 15(4):55–70, 2024.

[34] R. P. Singh and A. K. Pattnaik. Scientific insights into hyperlipidemia mitigation: A profound examination of isolated bioactive fractions of kalanchoe pinnata leaves and their therapeutic implications using in vitro, in vivo, and in silico study. *Pharmacognosy Magazine*, pages 1–14, 2024.

[35] D. Ramírez and J. Caballero. Is it reliable to take the molecular docking top scoring position as the best solution without considering available structural data? *Molecules*, 23(5):1038, 2018.

[36] V. N. Maiorov and G. M. Crippen. Significance of root-mean-square deviation in comparing three-dimensional structures of globular proteins. *Journal of Molecular Biology*, 235(2):625–634, 1994.

[37] M. F. Adasme et al. Plip 2021: Expanding the scope of the protein-ligand interaction profiler to dna and rna. *Nucleic Acids Research*, 49(W1):W530–W534, 2021.

[38] B. Q. Wei, W. A. Baase, L. H. Weaver, B. W. Matthews, and B. K. Shoichet. A model binding site for testing scoring functions in molecular docking. *Journal of Molecular Biology*, 322(2):339–355, 2002.

[39] A. Rausell, D. Juan, F. Pazos, and A. Valencia. Protein interactions and ligand binding: From protein subfamilies to functional specificity. *Proceedings of the National Academy of Sciences USA*, 107(5):1995–2000, 2010.

[40] M. L. Verdonk, P. N. Mortenson, R. J. Hall, M. J. Hartshorn, and C. W. Murray. Protein-ligand docking against non-native protein conformers. *Journal of Chemical Information and Modeling*, 48(11):2214–2225, 2008.

[41] R. Jagannathan. Characterization of drug-like chemical space for cytotoxic marine metabolites using multivariate methods. *ACS Omega*, 4:5402–5411, 2019.

[42] A. Daina and V. Zoete. A boiled-egg to predict gastrointestinal absorption and brain penetration of small molecules. *ChemMedChem*, 11(11):1117–1121, 2016.

[43] S. Y. M. Lim, J. S. E. Loo, M. Alshagga, M. A. Alshawsh, C. E. Ong, and Y. Pan. In vitro and in silico studies of interactions of cathinone with human recombinant cytochrome p450 enzymes. *Toxicology Reports*, 9:759–768, 2022.

[44] J. X. Qiu, Z. W. Zhou, Z. X. He, X. Zhang, S. F. Zhou, and S. Zhu. Estimation of the binding modes with important human cytochrome p450 enzymes, drug interaction potential, pharmacokinetics, and hepatotoxicity of ginger components using molecular docking, computational, and pharmacokinetic modeling studies. *Drug Design, Development and Therapy*, 9:841–866, 2015.