DOI: 10.55522/jmpas.V13I1.5903 **ISSN NO. 2320 – 7418**

International peer reviewed open access journal

Journal of Medical Pharmaceutical and Allied Sciences

Journal homepage: www.jmpas.com CODEN: JMPACO

Research article

In-silico approach: predictive ADME/T properties and ACE inhibitory action of isolated compounds of *Aspidopterys sps*

Udaya Chandrika P*[1], Sunitha K[1]

Department of Pharmacognosy, GITAM School of Pharmacy, GITAM Deemed to be University, Vishakapatnam, Andhra Pradesh, India

Corresponding author: Udaya Chandrika P, ✉ chandrika.uday.18@gmail.com, **Orcid Id**: https://orcid.org/0009-0001-5232-8919

Department of Pharmacognosy, GITAM School of Pharmacy, GITAM Deemed to be University, Vishakapatnam, Andhra Pradesh, India.

Received - 17-11-2023**, Revised** - 27-12-2023, **Accepted** - 18-01-2024 **(DD-MM-YYYY)**

Refer This Article

Udaya Chandrika P, Sunitha K, 2024. *In-silico* approach: Predictive ADME/T Properties and ACE inhibitory action of Isolated compounds of *Aspidopteryssps*. Journal of medical pharmaceutical and allied sciences, V 13 - I 1, Pages- 6377 – 6384. Doi: https://doi.org/10.55522/jmpas.V13I1.5903.

ABSTRACT

The current research study aimed to study Isolated phytocompounds of Aspidopterys sps (*A. indica* and *A.cordata*) by invitro antihypertensive activity, in-silico molecular docking, and ADME/T analysis. The preceding reports had revealed a fact of polyphenols and triterpenoids have an ability to control blood pressure by inhibition of Angiotensin converting enzyme (ACE). The isolated ligands Catechin, Isoorientin, Fisetin, and Ursolic acid (A , B, C and D) tested for ACE inhibition, docked with target Human Angiotensin-converting enzyme employing Autodock 4.2, drug-likeliness, physicochemical nature, toxicity prediction by Swiss ADME, ProTox tools available online. All phytoconstituents showed optimistic dose-responsive inhibition, Compounds exhibited magnificent IC_{50} (15.38 ± 0.53) µg/ml, B (20.21± 0.34 µg/ml), C (17.62 ± 0.78 µg/ml), D (23.98 ± 0.65 µg/ml), Captopril (15.86±0.32 µg/ml). Molecule A showed utmost binding energy (-7.3 K.cal/mol) significant alignment with target protein and good interactions compared to Captopril (-6.7) and Lisinopril (-7.38 K.cal/mol). Prediction of ADME/T and ligands showed good pharmacokinetic properties characterized by high absorption in the gastrointestinal tract, oral bioavailability, and minimal toxicity and high binding energies, so these bioactive compounds could be further explored as possible antihypertensive drugs.

Keywords: Aspidopterys sps, Isolated compounds, Docking, ADME, Toxicity prediction

INTRODUCTION

A significant health concern, high blood pressure is becoming more common in many nations. The ACE is an essential element of the RAS system, whose; primary function is the conversion of angiotensin I (Ang I) into angiotensin II (Ang II)[1].ACE inhibitors are considered one of the most effective cardiovascular disease treatments. Therefore, it can regulate and control high blood pressure and is often used to treat cardiovascular diseases[2]. Several studies have shown that polyphenols and triterpenes possess various biological and medicinal properties in combating human diseases, such as antioxidant, anti-atherosclerotic, antihypertensive, and anti-inflammatory effects [3-5]. Flavonoids are heterogeneous polyphenolic compounds that reduce blood pressure and inhibit ACE activity *in-vivo* and *in-vitro*[6,7].ACE inhibition is necessary for treating high blood pressure; some plant-based ACE inhibitors positively affect health[6]. Recently, the *in-silico* approach has been found to help study the molecular mechanism of phytochemicals and identify targets involved in particular diseases[8]. The reality that many drugs fail to reach the public due to poor pharmacokinetic profiles has made it necessary to include these aspects in the initial levels of drug development programs. It requires a search for lead compounds readily absorbed after oral administration and delivered to the required site of action. They are not quickly metabolized into toxic products before reaching the target and are readily excreted from the body to accumulate in amounts sufficient to cause negative consequences. The summary of the above activities is frequently mentioned as ADME properties[9].

In this way, molecular docking and pharmacokinetics studies covered the "drug-likeness" of compounds using Lipiński's rule of five, which helps to understand drug properties and interactions and minimize the risk before clinical trials[10]. Phytochemicals Catechin, Isoorientin, Fisetin, and Ursolic acid were isolated from *Aspidopteryss*ps family Malphigiaceae [11,12].Although polyphenols and triterpenoids are proven to have strong blood pressure-regulating potential, constituents identified from *Aspidopteryssps* are not investigated extensively for their pharmacological actions; the study aimed to establish the traditional assertion of antihypertensive potential; [12] using molecular docking simulations and to perform drug-likeness and ADME prediction for isolated compounds.

METHODOLOGY

Assessment of ACE Inhibitory activity

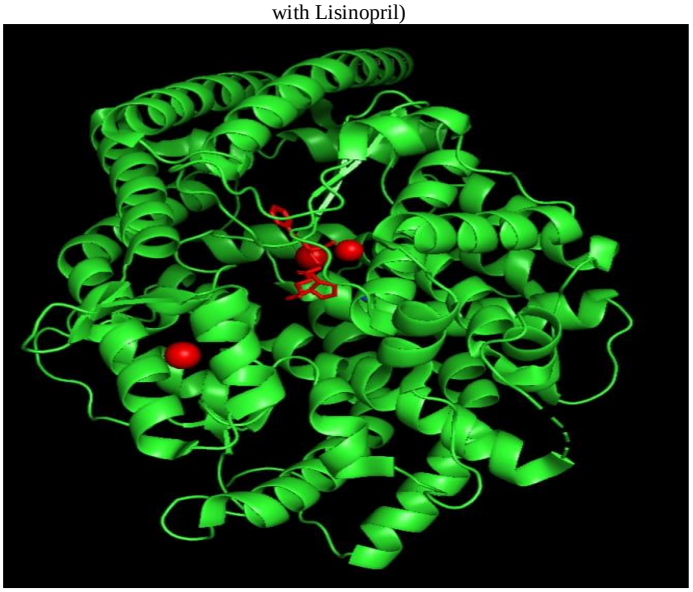
The inhibitory action of isolated compounds was performed using the Cushman-Cheung method[13,14].ACE inhibitor activity, hippurylhistidylleucine (HHL), the ACE hydrolyzes HHL into HA. Using a (UV-vis spectrophotometer, the HA has been measured at the wavelength of 228 nm to define the ACE activity. When an ACE inhibitor is expressed, the concentration of HA generated is diminished. The test solution (50 L) was made from the isolated fractions/standard using phosphate buffer (200 L, pH 8.3), sodium chloride (0.2 M), and Hippuryl-histidyl-leucine (HHL, 6.5mM). This mix was incubated at 37°C for 30 min using ACE solutions (100 µL), and the reaction's development was stalled by adding 1 M HCl (50 µL). Hippuric acid was separated from the reaction mixture using ethyl acetate, followed by centrifugation and vacuum evaporation of the eluent. A spectrophotometer was used to measure the absorbance of the final product at 228 nm, and the ACE inhibition activity has been calculated as follows: $\%\ Inhibition = \frac{Aa-Ab}{Aa-AC} X100$

Aa is the absorbance with ACE and HHL without the sample, Ab is the absorbance with ACE, HHL, and the sample or standard, and Ac is the absorbance with HHL without ACE and the sample (control)

Preparation of Ligand

Three-dimensional (3D) structures of all components acquired from PubChem. All structural metadata of the isolated compounds were retrieved from the database available on the National Center for Biotechnology Information (NCBI)website (http://pubchem.ncbi.nlm).nih.gov) [15], The structure files were made available in the required Protein Data Bank format (PDB) with the help of UCSF Chimera 1.1.4. 3D structures of Angiotensin-converting Enzyme associated with Lisinopril (Figure 1).

Figure 1: 3D imaging (Human Angiotensin-converting Enzyme associated with Lisinopril)

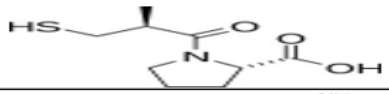
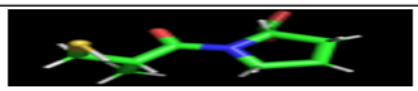
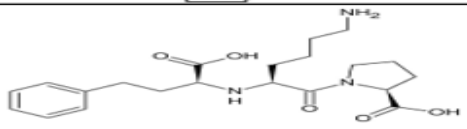
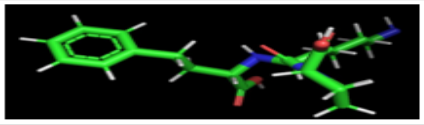
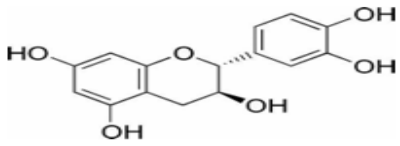
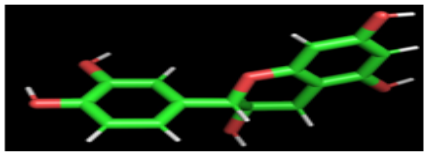
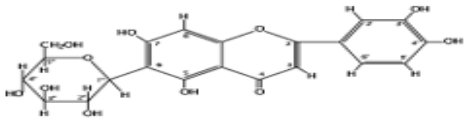
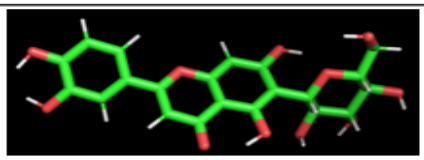
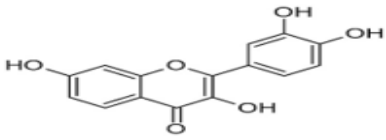
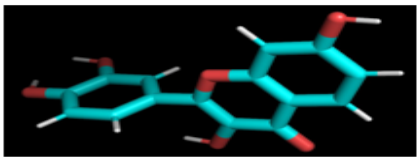
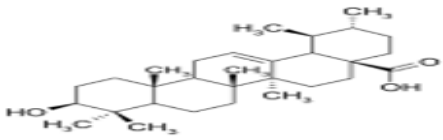
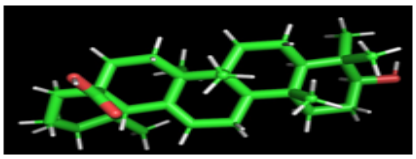


Target Protein data

The structural data of the Angiotensin-converting enzyme (in complex with Lisinopril) (PDB ID: 1O86) were obtained from the database (http://www.rcsb.org/pdb). Target Protein was selected based on a literature survey[16,17]. The molecular docking study was performed using the AutoDock 4.1 and Grid frame of (25 × 25 × 25) Å centered at (−19.415 × 74.650 × 33.857) Å with a grid spacing of 0.375 Å was used as default parameter binding affinity was examined using View Dock. The PDBQT format was created from the PDB files previously created for Ligand. After creating gpf (lattice parameter file) and dpf (docking parameter file), phyto compounds docking studies done to create the protein-ligand complex, then analysed and confirmations of the ideal dock site with the highest binding energy (BE, Kcal/mol) is noted[18]. Docked complexes and Aminoacids interactions were visualized using the BIOVIA Discovery Study Viewer[19].

A free online program called http://www.swissadme.ch was used for in silico ADME screening and drug-likeness assessment, and the Pro Tox-II online database was used to predict phytochemical toxicity (https://tox-new.charite.de/protox_II)[20]. By providing SMILES data, the ADME/T outcomes of the ligands were predicted, and the necessary data was generated. Lipiński has created a drug candidate (2001). Ghose (1999), Veber (2002), Egan (2000), and Muegge (2001) Abott bioavailability were calculated to estimate the compound probability having an oral bioavailability of at least 10% based on total loading, TPSA, and Lipinski filter violation. Lipophilicity has been implemented using iLOGP, XLOGP3, WLOGP, and MLOGP SILICOS IT log Po/w can be found[21]. Solubility(log S) selected ligands were implemented by three different models: ESOL[22, 23] and SILICOS-IT [24].

Figure.2: 2D and 3D images of Reference and Isolated compounds:

Compound	2-Dimentional Images	3-Dimensional Images
Captopril		
Lisinopril		
Catechin		
Isoorientin		
Fisetin		
Ursolic acid		

RESULTS AND DISCUSSION (*In-vitro* ACE Inhibition)

All Compounds showed dose dependent inhibition, compound an exhibited highest IC50 (15.38 ± 0.53 µg/ml), C (17.62 ± 0.78), B (20.21± 0.34) and D (23.98 ± 0.65 µg/ml). A-Catechin, B-Isoorientin, C-Fisetin, D-Ursolic acid Docking scores binding energies and amino acid residue interactions are represented in Table.2

Table.1: Effect of Isolated compounds on ACE inhibition

Concentration µg/ml	% ACE Inhibition				
	A	B	C	D	Captopril
5	20.89± 1.22	15.84± 0.15	19.46± 0.43	17.34± 1.01	21.89± 0.98
10	32.82± 0.89	23.54± 0.22	25.33± 0.76	24.47± 0.64	36.82± 0.76
15	45.34± 1.32	39.83± 0.89	42.65± 0.54	30.39± 0.56	45.34± 0.65
20	55.32± 0.89	51.43± 0.45	58.23± 0.62	41.14± 0.97	59.32± 0.46
25	63.43± 0.33	59.37± 0.46	69.43± 0.31	54.63± 0.55	75.43± 0.57
IC_{50} µg/ml	15.38 ± 0.53	20.21± 0.34	17.62 ± 0.78	23.98 ± 0.65	15.86±0.32

Table.2: Isolated molecules Binding Energies with target protein (PDB ID: 1O86) and Affinities with amino acids

Compound	Binding energy(Kcal/mol)	Pub chem ID	Category	Type
Captopril	-6.7	44093	H-Bond	Con. H-bond
			Hydrophobic	Pi-Sulfur
			Hydrophobic	Pi-alkyl
Lisinopril	-7.38	5362119	Hydrophobic	Water H-bond
			H-Bond	Con H-bond
			H-Bond	Covalent bond
			Hydrophobic	Pi-sigma
A	-7.3	9064	H-Bond	Con H-bond
			Hydrophobic	Pi-alkyl

			Hydrophobic	Pi-Pi
B	-6.61	5281614	H-Bond	Con.H-bond
			Hydrophobic	Pi-alkyl
C	-6.49	114776	H-Bond	Con. H- bond
			Hydrophobic	Pi-Pi
D	-3.81	64945	Hydrophobic	Pi-alkyl

Con H-bond-Conventional H-bond

Figures 3, 4, and 5 depict the existing molecular docking poses and interactions. When compared to conventional Lisinopril (-7.38) and Captopril (-6.7), A (the isolated chemical) had the highest binding energy (-7.3), while B (-6.61) exhibited equivalent binding energies to those of Captopril. D (-3.81) showed the lowest binding energy among all compounds. A shows binding with ACE protein with amino acids like, TRY.520, GLU.384, HIS.383, HIS.523, VAL.518, and HIS.353 with one hydrogen bond. B binds with VAL.379, HIS.383, GLU.384, HIS.387, GLU.411, ASP.453, VAL.380, ALA.354, and HIS.353with Convention hydrogen bond and Carbon hydrogen bond, C with ASP.453, GLN.281, PHE.527, TYR.523, GLU.411, TYR.520, HIS.513, and GLU.384with two hydrogen bonds. Captopril with GLU.384, ALA.354, HIS.383, HIS.353, PHE.457, LYS.511, GLN.281, TYR.520, and TYR523 with one hydrogen bond. Lisinopril with HIS.383, TYR.520, GLU.384, ALA.354, HIS.387, HIS.353, TYR.523, LYS.511.

Figure 3. Docking pose, Amino acid interactions of Captopril and Lisinopril with Human Angiotensin enzyme

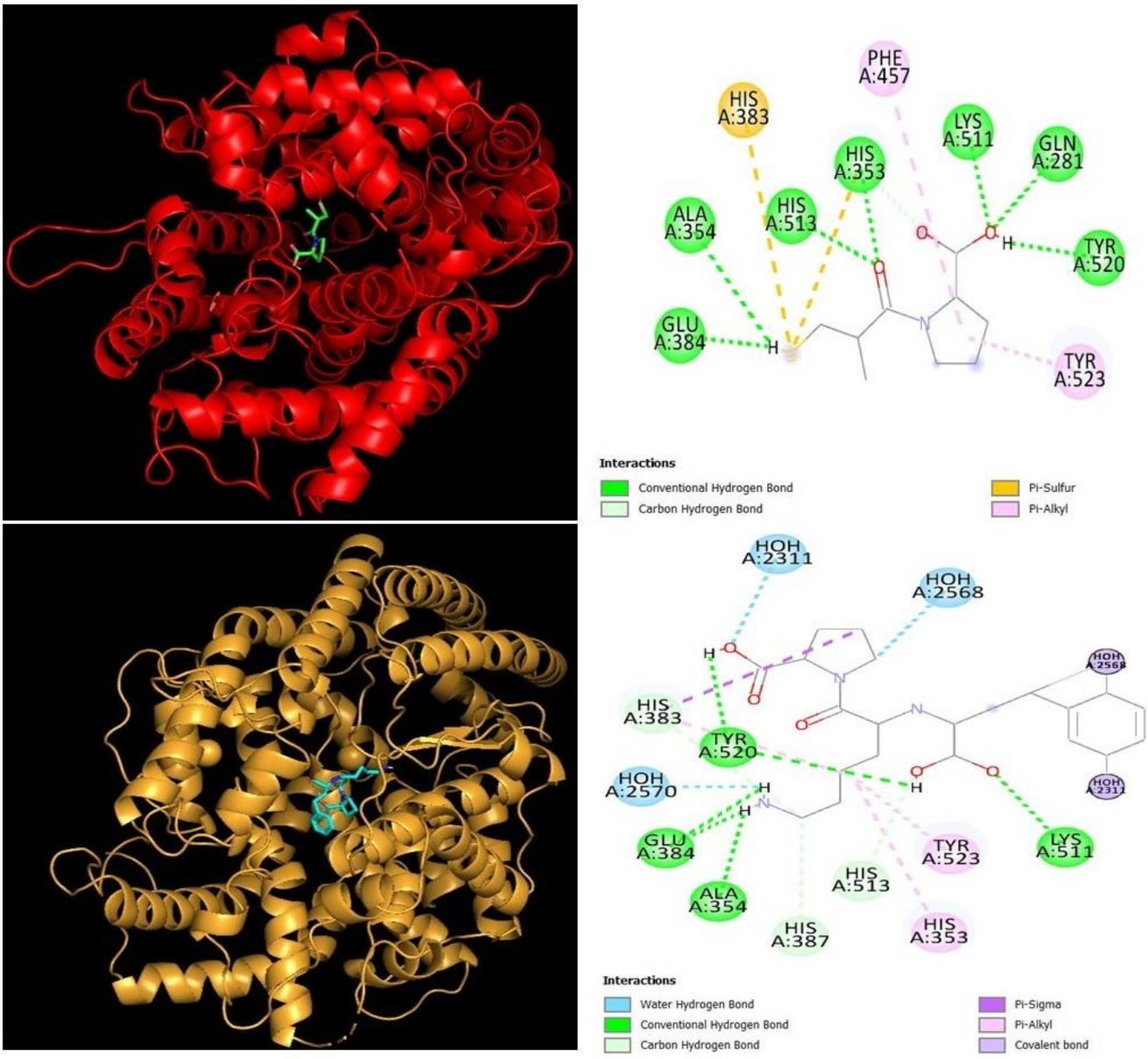


Figure 4: Docking pose, Amino acid interactions of Captopril and Lisinopril with Human Angiotensin enzyme

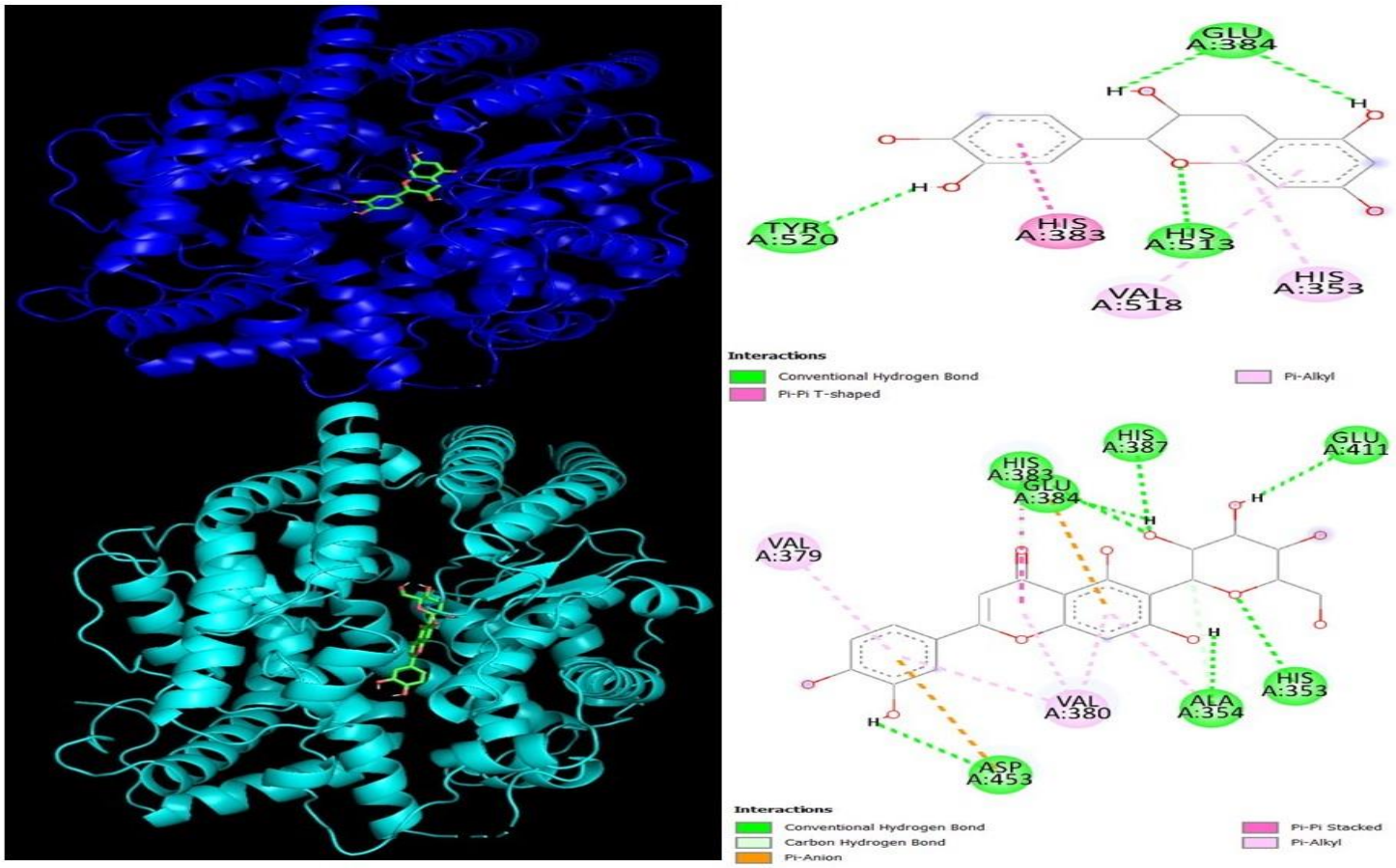
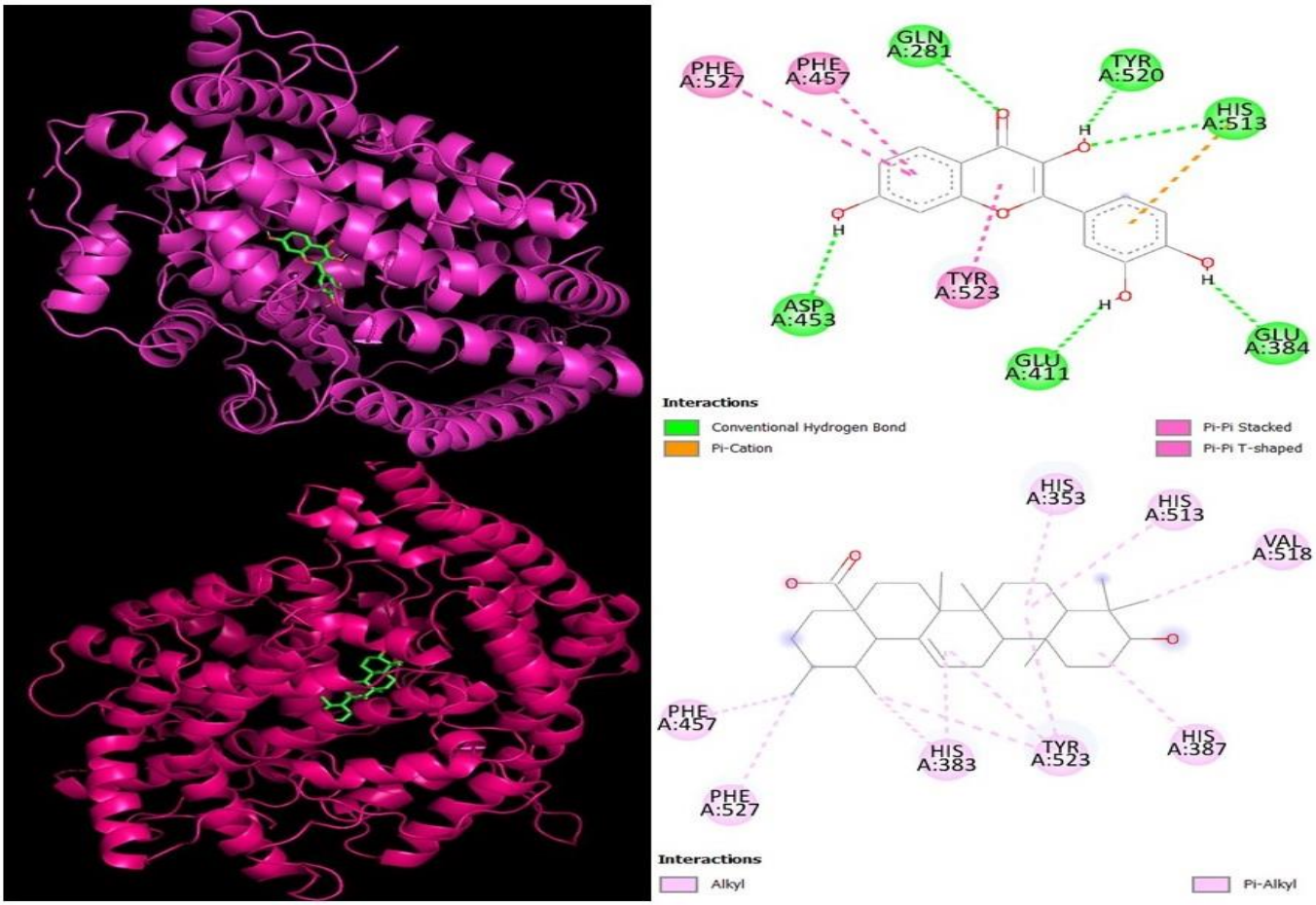


Figure 5: Docking pose visualization, Amino acids interactions of Catechin and Isoorientin with Human Angiotensin enzyme



Physicochemical properties

Basic Molecular parameters of isolated bio compounds

Elemental physicochemical properties showed promising results represented in Tables 3-5.

The molecular mass of the isolated components ranged from 290 to 460 g/mol. The calculated consensus log P is between 0.83 and 0.56, except that B had a negative Lipophilicity of −0.34.

Table 3. Summary of Isolated compounds physicochemical description

	A	B	C	D
Formula	$C_{15}H_{14}O_6$	$C_{21}H_{20}O_{11}$	$C_{15}H_{10}O_6$	$C_{30}H_{48}O_3$
MW	290.27	448.38	286.24	456.7
Heavy atoms	21	32	21	33
Ar. heavy atoms	12	16	16	0
Fr Csp3	0.2	0.29	0	0.9
Rotatable bonds	1	3	1	1
H-bond acceptors	6	11	6	3
H-bond donors	5	8	4	2
MR	74.33	108.63	76.01	136.91

Ar-Aromatic, Fr-Fraction

ADME Descriptors

The consequences of the predicted ADME results are presented in Table 6. Biocompounds A and C have high absorption in the gastrointestinal tract, and B and D have low absorption. No compound has BBB penetration. Compound A can inhibit Pgp. C has been shown to inhibit CYP1A2, CYP2D6, and CYP3A4 isoforms. A, B, D showed no inhibition of CYP-isoforms.

Summary of Drug Likeliness of Isolated Compounds

The drug probabilities for compounds are listed in Table 7. No Lipiński violations were reported for compounds A and C. B showed violations for 5 filters (Lipinski, Ghose, Veber, Egan, Mugge). Except for compound B (0.17) Bioavailability was between 55 and 85% of the probability class.

Table 4: Summary of Isolated compounds Lipophilicity:

	A	B	C	D
E. Log S	-2.22	-2.7	-3.35	-7.23
E. Solubility (mg/ml)	1.74E	9.00E-01	1.27E-01	2.69E-05
E. Solubility (mol/l)	5.98E-03	2.01E-03	4.43E-04	5.89E-08
E. Class	Sol	Sol	Sol	Poorly sol
Ali Log S	-2.24	-3.62	-3.93	-8.38
Ali Solubility (mg/ml)	1.66E+00	1.07E-01	3.37E-02	1.92E-06
Ali Solubility (mol/l)	5.72E-03	2.39E-04	1.18E-04	4.21E-09
Ali Class	Sol	Sol	Sol	Poorly. sol
Si.LogSw	-2.14	-1.79	-3.82	-5.67
Si.Solubility (mg/ml)	2.09E+00	7.32E+00	4.29E-02	9.72E-04
Si.Solubility (mol/l)	7.19E-03	1.63E-02	1.50E-04	2.13E-06
Si.class	Sol	Sol	Sol	Moderately. sol

Sol-Soluble**,** Silicos-IT-Si, E-ESOL

Table 5: Summary of Predicted water solubility of isolated compounds

	A	B	C	D
TPSA	110.38	201.28	111.13	57.53
iLOGP	1.33	1.6	1.5	3.95
XLOGP3	0.36	-0.15	1.97	7.34
WLOGP	1.22	-0.53	2.28	7.09
MLOGP	0.24	-2.51	-0.03	5.82
Silicos-IT Log P	0.98	-0.14	2.03	5.46
Consensus Log P	0.83	-0.34	1.55	5.93

Table 6: Summary of Prognostic ADME predictions of Isolates

	A	B	C	D
GI absorption	High	Low	High	Low
BBB permeant	N	N	N	N
Pgp substrate	Y	N	N	N
CYP1A2 inhibitor	N	N	Y	N
CYP2C19 inhibitor	N	N	N	N
CYP2C9 inhibitor	N	N	N	N
CYP2D6 inhibitor	N	N	Y	N
CYP3A4 inhibitor	N	N	Y	N

Y-Yes, N-No

Table 7: Prognostic Drug Likeliness of Isolated compounds

	A	B	C	D
log Kp (cm/s)	-7.82	-9.14	-6.65	-3.87
Lipinski violations	0	2	0	1
Ghose violations	0	1	0	3
Veber violations	0	1	0	0
Egan violations	0	1	0	1
Muegge violations	0	3	0	1
Bioavailability Score	0.55	0.17	0.55	0.85

Table 8: Summary of Toxicity Prediction of Phytochemica

Ligand	LD50 (mg/kg)	Toxicity class	Hepato toxicity	Immuno toxicity	Cytotoxicity	Carcinogenicity
A	10,000	6	In-A	In-A	In-A	In-A
B	159	3	In-A	In-A	In-A	In-A
C	159	3	In-A	In-A	In-A	A
D	2,000	4	In-A	A	In-A	In-A

Toxicity Prediction

The results on LD_{50}, mutagenicity, carcinogenicity and toxicity class of the isolated ligands are shown in Table 8. The ligands B, C belong to class 3, where A is assigned to class 6 and D to class 4. It has been proven that carcinogenicity be active. In C, while immunogenicity is active in D In A Active.

CONCLUSION

This study examined the compounds that were identified from active subfractions of *Aspidopterys*sps were screened individually for assessing the pharmacokinetic parameters and antihypertensive potential using in silico techniques such as molecular docking and ADME/T prediction. The results confirmed the promising results of blood pressure-lowering efficacy of isolated compounds and strong binding affinity with the target protein (human angiotensin-converting enzyme) compared to the reference drug captopril. In addition, drug-likeness studies and compound toxicity prediction studies have demonstrated increased antihypertensive potential. Additionally individual assessment of compounds for their antihypertensive effect, specific effect, Mechanism of action and optimization are scopes of future research

ACKNOWLEDGMENT

The authors are thankful to GITAM School of Pharmacy for encouragement and possible support.

Conflict of interest

There is no conflict of interest

REFERENCES

1. Ondetti MA, Rubin B, Cushman DW. 1977. Design of specific inhibitors of angiotensin-converting enzyme: New class of orally active antihypertensive agents. Science 4288 (196), Pages- 441–444. Doi: https://doi.org/10.1126/science.191908.

2. Ra JE, Woo SY, Jin H, et al, 2020. Evaluation of antihypertensive polyphenols of barley (Hordeumvulgare L.) seedlings via their effects on angiotensin-converting enzyme (ACE) inhibition. Applied Biological Chemistry 63, 38 Doi: https://doi.org/10.1186/s13765-020-00519-9.

3. Hai-Bang T, Shimizu K. 2015. Structure–activity relationship and inhibition pattern of reishi-derived (Ganodermalingzhi) triterpenoids against angiotensin-converting enzyme. Phytochemistry Letters 12, Pages- 243-247. Doi: https://doi.org/ 10.1016/j.phytol.2015.04.021.

4. Choi S, Seo HS, Lee KR, et al, 2018. Effect of cultivars and milling degrees on free and bound phenolic profiles and antioxidant activity of black rice. Applied Biological chemistry 61, Pages- 49–60. Doi: https://doi.org/10.1007/s13765-017-0335-3.

5. Cédric G, Robert B, Yannick M. 2004. Dietary Polyphenols Increase Paraoxonase 1 Gene Expression by an Aryl Hydrocarbon Receptor-Dependent Mechanism, Molecular and Cellular Biology 24 (12), Pages- 5209-5222. Doi: 10.1128/MCB.24.12.5209-5222.2004.

6. Actis-Goretta L, Ottaviani I, Keen CL, et al, 2003. Inhibition of angiotensin converting enzyme (ACE) activity by flavan-3-ols and procyanidins. FEBS Letters 555 (3), Pages- 597-600. Doi: https://doi.org/10.1016/S0014-5793(03)01355-3.

7. Muchtaridi M, Fauzi M, KhairulIkram NK, et al, 2020. Natural Flavonoids as Potential Angiotensin-Converting Enzyme 2 Inhibitors for Anti-SARS-CoV-2. Molecules 25 (17):3980. Doi: https://doi.org/10.3390/molecules2517398.

8. Ntie-Kang F, Lifongo LL, Mbah JA, et al, 2013. In silico drug metabolism and pharmacokinetic profiles of natural products from medicinal plants in the Congo basin. In Silico Pharmacology 1:12. Doi: https://doi.org/10.1186/2193-9616-1-1.

9. Guerrero L, Castillo J, Quiñones M, et al, 2012. Inhibition of Angiotensin-Converting Enzyme Actiity by Flavonoids: Structure-Activity Relationship Studies. PLOS ONE 7 (11), e49493. Doi: https://doi.org/10.1371/journal.pone.0049493.

10. Ya'u Ibrahim Z, Uzairu A, Shallangwa G, et al, 2020. Molecular docking studies, drug-likeness and in-silico ADMET prediction of some novel β-Amino alcohol grafted 1, 4, 5-trisubstituted 1, 2, 3-triazoles derivatives as elevators of p53 protein levels.ScientificAfrican 10, e00570. Doi: https://doi.org/10.1016/j.sciaf.2020.e00570.

11. ChandrikaPulla U, Katta S. 2023. Isolation and Characterisation of Bioactive Compounds from Methanolic Fraction of Aerial parts of Aspidopteryscordata. Journal of Population Therapeutics & Clinical Pharmacology 30 (14), Pages- 268-276. Doi: 10.47750/jptcp.2023.30.14.036.

12. Udaya chandrika P, Sunitha K. 2021. Pharmacognostic Evaluation, Estimation of Phenolic, Flavonoid Composition and Antioxidant Activity of Aspidopterysindica (Willd.)W.Theob: An Endemic Plant to Peninsular India. Annals of the Romanian Society for Cell Biology 25 (4), Pages- 13884-13891.

13. Paiva L, Lima E, Neto AI, et al, 2017. Angiotensin I-Converting Enzyme (ACE) Inhibitory Activity, Antioxidant Properties, Phenolic Content and Amino Acid Profiles of Fucusspiralis L. Protein Hydrolysate Fractions. Marine Drugs 15 (10). Doi: https://doi.org/10.3390/md15100311.

14. Udaya Chandrika P, Sunitha K. 2021. ACE Inhibitory Activity and Antihypertensive Effect of Aspidopterys Cordata in DOCA-Salt-Induced Hypertension In Rats. Natural Volatiles Essential Oils 8 (6), Pages- 4993-4999.

15. Yende SR, Shah SK, Arora SK, et al, 2021. In silico prediction of phytoconstituents from Ehretialaevis targeting TNF-α in arthritis. Digital Chinese Medicine 4 (3), Pages- 180-190. Doi: https://doi.org/10.1016/j.dcmed.2021.09.003.

16. Ononamadu CJ, Ibrahim A. 2021. Molecular docking and prediction of ADME/drug-likeness properties of potentially active antidiabetic compounds isolated from aqueous-methanol extracts of Gymnemasylvestre and Combretummicranthum. BioTechnologia 102 (1), Pages- 85-99. Doi: https://doi.org/10.5114/bta.2021.103765.

17. Mondal S, Talukdar P, Mondal TK.2018 Study of molecular docking to detect antihypertensive phytochemicals of Oxalis corniculata Linn. against angiotensin converting enzyme. World Sci News. Pages-42-55.

18. Anthony Ammal SM, Sudha S, Rajkumar D, et al, 2023. In Silico Molecular Docking Studies of Phytocompoundsfrom Coleus AmboinicusagainstGlucokinase. Cureus 15 (2). Doi: https://doi.org/10.7759/cureus.34507.

19. Vardhan S, Sahoo SK. 2020. In silico ADMET and molecular docking study on searching potential inhibitors from limonoids and triterpenoids for COVID-19. Computers in Biology and Medicine 124, 103936. Doi: https://doi.org/10.1016/j.compbiomed.2020.103936.

20. Banerjee P, Eckert AO, Schrey AK, et al, 2018. ProTox-II: A webserver for the prediction of toxicity of chemicals. Nucleic Acids Research 46 (W1), Pages- W257-W263. Doi: https://doi.org/ 10.1093/nar/gky318.

21. Daina A, Michielin O, Zoete V. 2017. SwissADME: A free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Scientific Reports 7. Doi: https://doi.org/10.1038/srep42717.

22. Delaney JS. 2004. ESOL: Estimating Aqueous Solubility Directly from Molecular Structure. Journal of Chemical Information Computer Sciences 44 (3), Pages- 1000-1005. Doi: 10.1021/ci034243x.

23. Ali J, Camilleri P, Brown MB, et al, 2012. Revisiting the general solubility equation: in silico prediction of aqueous solubility incorporating the effect of topographical polar surface area. Journal of chemical information and modeling 52 (2), Pages- 420–428. Doi: https://doi.org/10.1021/ci200387c.

24. Ni NyomanYuliani, Siswandono, TristianaErawati, JefrinSambara, Sandeep Poddar, Radhwan Hussein Ibrahim, 2023. Molecular docking of antioxidant activity of bougainvillea spectabilis wild bractea ethanol fraction with aryl hydro carbon inhibitors and vitamin C comparator. Journal of medical pharmaceutical and allied sciences, V 12 - I 6, Pages- 6274 – 6280. Doi: https://doi.org/10.55522/jmpas.V12I6.5946.