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MOLECULAR INTERACTIONS OF DIOSMIN AND HESPERIDIN WITH ANGIOTENSIN CONVERTING ENZYME 1 *IN-SILICO*.

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ABSTRACT:

Hypertension is a global health concern with increased morbidity and mortality. It is well-known that the angiotensin-converting enzyme 1 (ACE1) plays a crucial role in regulating blood pressure and hence targeted for the treatment of hypertension and hypertensive diseases. This study aims to understand the molecular interactions of diaosmin and hesperidin with ACE1. Both the phytochemicals diaosmin and hesperidin were found to be present in *Artocarpus altilis* leaf, as evident from the HR-LCMS analysis. The diosmin and hesperidin were analyzed for their binding affinities for the active site of human ACE1 (PDB1086) by *in silico* molecular docking. Diosmin and hesperidin exhibited higher binding affinities for ACE1 active site, with the binding energy of -13.8 and -13.1 kcal/mol, respectively. Diosmin interacted with amino acid residues such as His353, Gln281, Val379, His383, Tyr523, Zn701, His410, and His513, whereas hesperidin interacted with Gln281, His353, His513, Tyr523, Zn701, His383, His410, Val379, and Glu376. These results suggest the stronger binding of diosmin and hesperidin to the ACE1, and offer their therapeutic potential. Further investigations to understand their therapeutic benefits in managing hypertensive diseases are essential.

Keywords: diosmin, hesperidin, hypertension, ACE1, breadfruit

1. INTRODUCTION

Angiotensin-converting enzyme 1 (ACE1) is a dipeptidyl carboxypeptidase that controls blood pressure by participating in the renin-angiotensin system. ACE1 inhibition has been considered one of the effective therapeutic approaches for the management of hypertension and cardiovascular diseases. Currently, available ACE1 inhibitory drugs exhibit several side effects, including angioedema, hyperkalemia, dry cough, angioedema, hypotension, dizziness, headache, and renal, despite their therapeutic benefits (Pinto et al., 2020). Of note, the medicinal plants have gained importance due to their better cultural acceptability, compatibility with the human body, and fewer side effects (Siddesha et al., 2010)

Artocarpus altilis (Park.) Fosb, commonly known as 'breadfruit,' is widely distributed in tropical and subtropical regions, including India. It is one of the medicinally important plants belonging to the family "Moraceae." *A. altilis* is one of the multipurpose trees with a wide range of traditional uses as food, medicine, and a source of materials. The leaves are used for the treatment of liver disorders, hypertension, diabetes, kidney failures, fevers, wound healing, and to reduce cholesterol. In folk medicine, the decoction of the leaves has been used for the treatment of hypertension, high cholesterol, urinary problems, jaundice, and diabetes (Raju et al., 2017). The preliminary screening study of *A. altilis* leaf extracts has given promising experimental evidence of ACE1 inhibitory activity and justified the traditional use of *A. altilis* leaf for the treatment of hypertension (Siddesha et al., 2011, Nwokocha et al., 2017).

Diets rich in flavonoids have been shown to enhance cardiovascular parameters, and long-term dietary supplementation with hesperidin and glucosyl hesperidin resulted in the normalization of heart rate and blood pressure in spontaneously hypertensive rats (Yamamoto et al., 2013). Also, treatment with hesperidin increased nitric oxide inactivation and safeguarded endothelial function in stroke-prone spontaneously hypertensive mice. Diosmin is currently one of the most sought-after natural compounds in the treatment of various diseases, including chronic venous insufficiency. Diosmin has been demonstrated to possess anti-oxidant properties, which enable it to effectively regulate the activities of several variables such as enzymes and biomarkers, linked to oxidative imbalance in diseases (Feldo et al., 2019).

The current study was designed to explore the molecular interactions of diosmin and hesperidin with ACE1 *in silico* molecular docking studies.

2. MATERIAL AND METHODS

2.1 Molecular docking

2.1.1 Protein and ligand selection and preparation

The crystal structure of human ACE1 in complex with lisinopril (PDB ID: 1O86) was used for the investigation. The chosen protein was prepared by removing lisinopril from its active site and adding polar hydrogen molecules to its whole structure. The structure Lisinopril, diosmin, and hesperidin were downloaded from the PubChem, NCBI. The obtained structures chemical ID, molecular formula were noted. Then the downloaded structures are translated into PDB file format and loaded to the PyRx for molecular docking using open babel software.

2.1.2 Molecular Docking Analysis

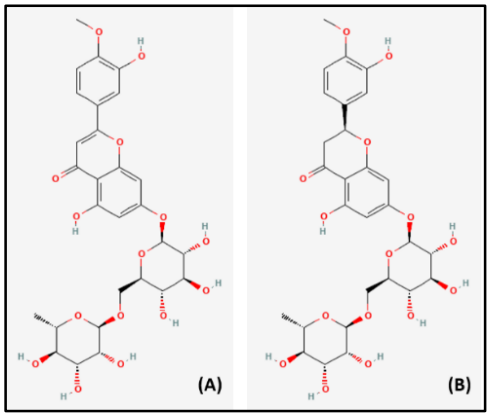
Molecular docking studies were conducted using the Autodock Vina program to understand the interactions between proteins and the ligands. The proteins and ligands were loaded in PDB format, and the active site residues were marked to define the grid box. The highest orientation with the lowest binding affinity (Kcal/mol) values was obtained.

2.1.3 Visualization: The docked conformation of the ligands against the proteins was visualized using Pymol. This program created 3D visualizations of the interactions between protein and compound, including hydrogen bonds, hydrophobic interactions, and bond length**.**

3. RESULTS

3.1 Structures of ligands

The ligand structures of diosmin (A) (Pubchem ID - 5281613) and hesperidin (B) (Pubchem ID – 10621) were downloaded from the PubChem, NCBI.



3.2. Molecular docking for screening of potent ACE inhibitor

The diosmin and hesperidin were considered as ligands and docked against ACE1 to explore their molecular interactions. The results of the molecular docking between the ACE1 and the compounds are presented in Table 1. The best-docked pose with the lowest binding affinity (Kcal/mol) values, along with the binding ability to zinc ion at the active site of ACE1, was considered. The docking results of diosmin and hesperidin showed the binding ability to zinc ions with the lowest binding energy. The interactions between all listed ligands and the proteins were analyzed using Pymol software, highlighting the key binding residues. The selected ligands were observed to form hydrogen bonds with the protein and were also partially surrounded by hydrophobic interactions.

Table 1: Interaction details of the ligands with ACE1.

Compound	Affinity (kcal/mol)	Hydrogen bond sites	Other interactions
Diosmin	-13.8	His353, Gln281	Val 379, His 383, Tyr 523, Zn 701, His 410,His 513
Hesperidin	-13.1	His353, Gln281	His 513, Tyr 523, Zn 701, His 383, His 410, Val 379, Glu376

In silico molecular docking study revealed that the troxerutin had the highest binding score, indicating a strong binding affinity for the ACE1 but no interaction to the active site However, hesperedin and diosmin showed the binding to zinc ion with lowest energy. Hesperidin and diosmin showed several hydrogen bonds with key amino acid residues, most importantly, an interaction with zinc ions at the active site of the ACE1 (Figure 1). Docked with ACE1 and their orientation.

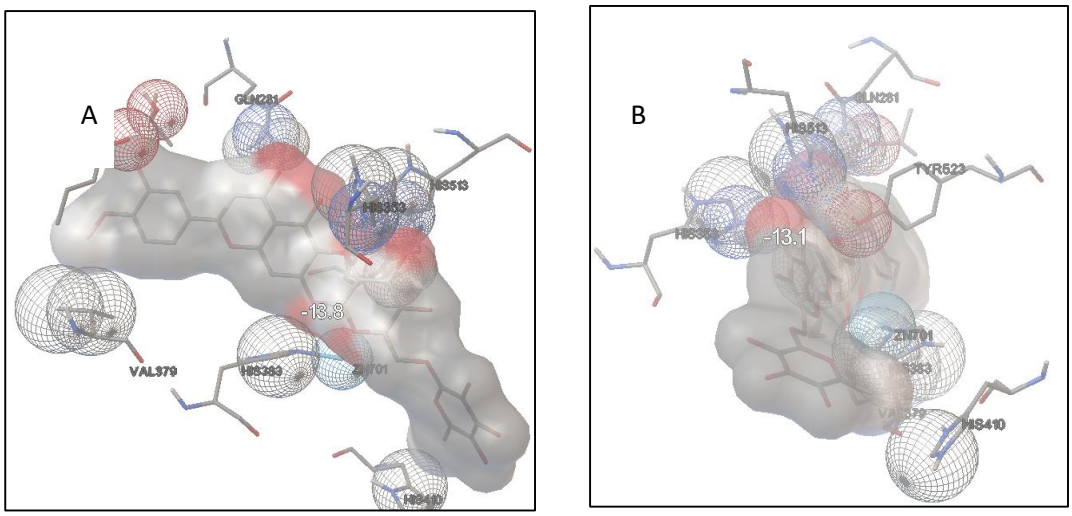


Figure 1: Three-D structures of Diosmin (A) and Hesperidin (B)

Both the diosmin and hesperidin exhibited greater binding affinities as per affinity scores -13.8 and -13.1 kcal/mol respectively. Diosmin interacted with amino acid residues such as His353, Gln281, Val379, His383, Tyr523, Zn701, His410, and His513. Similarly, hesperidin interacted with Gln281, His353, His513, Tyr523, Zn701, His383, His410, Val379, and Glu376. These results suggest the binding of diosmin and hesperidin to the ACE1, revealing their therapeutic potential.

4. DISCUSSION

Plant-based medicinal systems have become popular in the modern era due to their low cost, ease of availability, effectiveness, and lack of adverse effects. In this study, we focus on validating potential of diosmin and hesperidin as ACE inhibitory phytocompounds from *A. altilis* leaf. The extract subjected to HRLCMS revealed the presence of diosmin and hesperidin in the *A. altilis* leaf extract. Further, diosmin and hesperidin were considered for the *in silico* molecular docking analyses due to their therapeutic potentials as discussed earlier. The data of molecular docking studies with ACE1 revealed that the doismin and hesperidin bind to the ACE1 with a strong binding energy (-13.8 and -13.1 kcal/mol) respectively (Table 1). Overall analysis showed that diosmin and hesperidin showed the interaction with the zinc metal and thus potent ACE inhibition. Similar binding pattern was observed in previous research data (Caballero, 2020). Among the two, diosmin showed higher binding affinities, and interacted with His353 and Gln281 residues and formed connections with Val379, His383, Tyr523, Zn701, His410, and His513. On the other hand, hesperidin showed a high propensity for binding to Gln281 and His353. The interactions seen during the docking procedure with hesperidin involved the amino acid residues His513, Tyr523, Zn701, His383, His410, Val379, and Glu376.

5. CONCLUSIONS

In conclusion, the virtual screening studies demonstrated that the diosmin and hesperidin have greater binding affinity for ACE1. Particularly, the binding interactions of both diosmin and hesperidin were with Zn701, which is essential for ACE1 activity. Altogether, diosmin and hesperidin are promising with potentials to be ACE1 inhibitors. Further investigations are necessary to understand their therapeutic benefits in the management of hypertensive diseases.

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Disclosure statement
The author declares that (s)he has no relevant or material financial interests that relate to the research described in this paper.

6. REFERENCE

1. Pinto B, Jadhav U, Singhai P, Sadhanandham S, Shah N. ACEI-induced cough: A review of current evidence and its practical implications for optimal CV risk reduction. Indian Heart J. 2020 Sep-Oct;72(5):345-350. doi: 10.1016/j.ihj.2020.08.007.
2. Siddesha JM, Angaswamy N, Vishwanath BS. Phytochemical screening and evaluation of in vitro angiotensin-converting enzyme inhibitory activity of Artocarpus altilis leaf. Nat Prod Res. 2011 Dec;25(20):1931-40. doi: 10.1080/14786419.2010.497962.
3. Nwokocha C, Palacios J, Simirgiotis MJ, Thomas J, Nwokocha M, Young L, Thompson R, Cifuentes F, Paredes A, Delgoda R. Aqueous extract from the leaf of Artocarpus altilis provides cardio-protection from isoproterenol-induced myocardial damage in rats: Negative chronotropic and inotropic effects. Journal of Ethnopharmacology. 2017 May 5;203:163-70.
4. Raju V, Bell JJ, Merlin NJ, Dharan SS. Ethno Pharmacological Uses of Artocarpus Altilis-A Review. Asian Journal of Pharmaceutical Research. 2017;7(4):239-43.
5. Siddesha JM, D'Souza CJ, Vishwanath BS. Inhibition of angiotensin-converting enzyme (ACE) by medicinal plants exhibiting antihypertensive activity. Drug plants III. 2010:269-308.
6. Caballero J. Considerations for Docking of Selective Angiotensin-Converting Enzyme Inhibitors. Molecules. 2020 Jan 11;25(2):295. doi: 10.3390/molecules25020295.
7. Yamamoto M, Jokura H, Suzuki A, Hase T & Shimotoyodome A, Effects of continuous ingestion of hesperidin and glucosyl hesperidin on vascular gene expression in spontaneously hypertensive rats. J Nutr Sci Vitaminol (Tokyo), 59 (2013) 470
8. Feldo, M., Wójciak-Kosior, M., Sowa, I., Kocki, J., Bogucki, J., Zubilewicz, T., Kęsik, J., & Bogucka-Kocka, A. (2019). Effect of diosmin administration in patients with chronic venous disorders on selected factors affecting angiogenesis. *Molecules*, *24*(18). https://doi.org/10.3390/molecules24183316.