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Molecular docking of alkaloid compounds from the pule pandak plant (*Rauvolfia serpentina* L.) as inhibitors of angiotensin-converting enzyme

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Abstract: Hypertension is a major global health issue requiring effective treatments with minimal side effects. The angiotensin-converting enzyme (ACE) is a key target in hypertension therapy, and plant-derived compounds are being explored as potential ACE inhibitors. The pule pandak plant (*Rauvolfia serpentina* L.) contains alkaloid compounds that may have antihypertensive properties. This study aimed to evaluate the potential of alkaloid compounds *(ajmaline, rescinnamine, reserpine, and serpentine)* from the pule pandak plant as antihypertensive agents using an *in silico* molecular docking approach. Molecular docking was conducted to analyze the binding affinity of the alkaloid compounds to the ACE protein (PDB ID: 1UZF). Binding free energy values were calculated using AutoDockTools software. The ajmaline-1UZF complex exhibited the lowest binding free energy (-5.89 kcal/mol), indicating the strongest binding affinity among the tested compounds. This suggests that ajmaline has the highest inhibitory potential for ACE.

Keywords: alkaloid, anti-hypertension, molecular docking, pule pandak

Introduction

According to data from the World Health Organization (WHO), approximately 1.13 billion people worldwide were living with hypertension in 2015, equating to 1 in 3 individuals globally. However, only 36.8% of those diagnosed received treatment. The prevalence of hypertension continues to rise each year, with projections estimating that by 2025, 1.5 billion people will be affected, and 9.4 million deaths annually will be attributed to hypertension and its complications. Hypertension is clinically defined as a condition in which systolic blood pressure exceeds 140 mmHg and diastolic blood pressure exceeds 90 mmHg [1]. If left uncontrolled, hypertension can lead to severe complications, including stroke, kidney failure, and coronary heart disease, underscoring the necessity for effective and sustained treatment [2].

In the search for effective treatments for hypertension, one of the key targets is the angiotensin-converting enzyme (ACE), a protein integral to blood pressure regulation in the human body. ACE facilitates the conversion of angiotensin I to angiotensin II, a compound that causes blood vessel constriction and raises blood pressure. Additionally, ACE degrades bradykinin, a vasodilatory compound that helps lower blood pressure [3]. Given the critical role of ACE in hypertension pathophysiology, the exploration of active compounds capable of inhibiting this enzyme has become a significant area of research, particularly in the development of antihypertensive drugs with improved potency and reduced side effects.

This study aimed to investigate the potential antihypertensive activity of alkaloid compounds from the *pule pandak* plant (*Rauvolfia serpentina* L.) using an *in silico* molecular docking approach. *In silico* methods, which employ computational tools to simulate and analyze biological interactions, offer several advantages, including cost-effectiveness, time efficiency, and the ability to predict the pharmacological mechanisms of candidate compounds [4][5].

The focus of this research was on four alkaloid compounds found in *pule pandak*: ajmaline, rescinnamine, reserpine, and serpentine. These compounds were evaluated for their potential as ACE inhibitors. Despite the known medicinal properties of *pule pandak*, no prior studies have explored its alkaloid compounds' antihypertensive potential using computational approaches. This study seeks to address this gap by

providing insights into the possible antihypertensive effects of *pule pandak* alkaloids, thereby contributing valuable information to the development of plant-based antihypertensive treatments.

Methods

Tools and materials

The molecular docking study was conducted using a personal computer (PC) with Windows 11 Home Single Language 64-bit specifications. The following software tools were utilized: Avogadro, AutoDockTools version 1.5.6, the RCSB Protein Data Bank (PDB) website (www.rcsb.org), and BIOVIA Discovery Studio 2021. The 3-dimensional structure of the target protein (PDB ID: 1UZF) was obtained from the RCSB Protein Data Bank.

Protein preparation

The selected target protein, the human testicular angiotensin I-converting enzyme (PDB ID: 1UZF), was downloaded from the RCSB Protein Data Bank (http://www.rcsb.org/). Protein preparation was performed using the AutoDockTools version 1.5.6 software. During this process, the protein was separated from its native ligands, and the desired protein chain was selected for subsequent analysis.

Compound preparation

The study focused on four alkaloid compounds derived from the *pule pandak* plant: ajmaline, rescinnamine, reserpine, and serpentine. The molecular structures of these compounds were downloaded from the MolView website (https://molview.org/) in .mol file format. These files were then converted into .pdb format using Avogadro software. Geometric optimization of the compounds was performed in Avogadro, after which the optimized structures were saved in .pdb format.

Molecular docking

Molecular docking simulations were performed to analyze the binding interactions between the selected compounds (ajmaline, rescinnamine, reserpine, and serpentine) and the 1UZF protein. This process was carried out using AutoDockTools version 1.5.6. The prepared protein and ligand files were saved in .pdbqt format and loaded into the software. The grid box parameters were set based on validation results, with dimensions of 10 × 10 × 12 and coordinates of x = 40.835, y = 34.382, and z = 44.607.

Interaction visualization

Protein-ligand interactions resulting from the molecular docking simulations were visualized using BIOVIA Discovery Studio 2021. This software was used to analyze and illustrate the binding interactions within the protein-ligand complexes.

Results

This study employed *in silico* computational techniques, specifically molecular docking, to predict the interactions between the target protein (1UZF) and selected alkaloid compounds. Molecular docking is a widely used method in drug discovery and development to evaluate the binding affinity of compounds to biological targets, such as proteins. In pharmaceutical research, this technique plays a crucial role in designing new drugs and optimizing existing ones [4].

Molecular docking simulations were conducted to evaluate the binding affinity of four alkaloid compounds (ajmaline, rescinnamine, reserpine, and serpentine) to the 1UZF protein. Prior to docking, method validation was performed using the native ligand (MCO) as a control to ensure the reliability of the docking protocol. The binding free energy values obtained from the molecular docking experiments are presented in Table 1.

Table 1. Binding free energy results for protein-compound complexes

Compound	Binding free energy (kcal/mol)
MCO (native ligand)	-5.72
Ajmaline	-5.89
Rescinnamine	+35.77
Reserpine	+7.83
Serpentine	+6.14

The results revealed that the binding free energy of the native ligand (MCO) to the 1UZF protein was -5.72 kcal/mol. Among the tested compounds, ajmaline demonstrated the lowest binding free energy value of -5.89 kcal/mol, suggesting it has a higher binding affinity to the 1UZF protein compared to the native ligand. This indicates that ajmaline has greater potential as an angiotensin-converting enzyme (ACE) inhibitor. In contrast, rescinnamine, reserpine, and

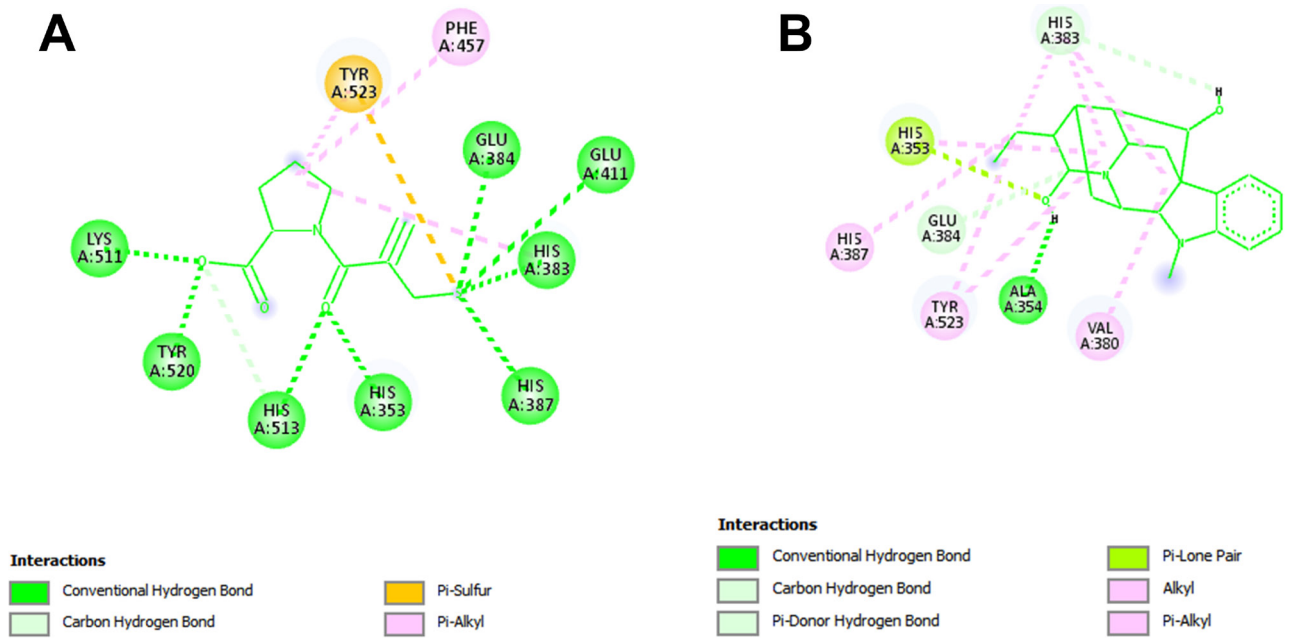

Figure 1. 2D visualization of ligands with 1UZF protein. (A) native ligand (MCO), (B) ajmaline

serpentine showed significantly higher binding free energy values (+35.77 kcal/mol, +7.83 kcal/mol, and +6.14 kcal/mol, respectively), indicating lower binding affinity compared to both MCO and ajmaline.

The interactions between the ligands and the 1UZF protein were visualized using BIOVIA Discovery Studio 2021 software. The 2D visualization of the native ligand (MCO) with the 1UZF protein revealed multiple types of interactions, including hydrogen bonds, Pi-sulfur, and Pi-alkyl bonds. Hydrogen bonds were observed with eight amino acid residues: GLU A:384, GLU A:411, LYS A:511, HIS A:383, HIS A:387, HIS A:353, HIS A:513, and TYR A:520. Additionally, a Pi-sulfur interaction was identified with the amino acid residue TYR A:523, and a Pi-alkyl interaction was observed with PHE A:457.

The 2D visualization of the ajmaline compound with the 1UZF protein revealed a variety of interactions, including hydrogen bonds, carbon-hydrogen bonds, Pi-donor hydrogen bonds, Pi-lone pairs, alkyl interactions, and Pi-alkyl interactions. Specifically, ajmaline formed a hydrogen bond with the amino acid residue ALA A:354, while a carbon-hydrogen bond was observed with the GLU A:384 residue. A Pi-donor hydrogen bond was identified involving HIS A:383, and a Pi-lone pair interaction was observed with HIS A:353. Additionally, alkyl interactions were formed with TYR A:523, while Pi-alkyl interactions were identified with HIS A:387 and VAL A:380.

Discussion

The evaluation of energy in the molecular docking process, as implemented in the AutoDock program, involves two critical steps. The first step estimates the intramolecular energy before and after docking, while the second step assesses the intermolecular energy following the physical binding of the ligand and the protein [6]. The intermolecular energy includes contributions from Van der Waals forces, hydrogen bonding, electrostatic interactions, and desolvation energy. To validate the docking method, the root mean square deviation (RMSD) value was used to compare the position of the initial ligand with the docking results. An RMSD value less than or equal to 2 Å is generally considered to indicate a valid docking method [7].

Among the tested compounds, the ajmaline-1UZF complex exhibited the lowest binding free energy value, suggesting that ajmaline has the highest potential as an antihypertensive compound. Lower binding free energy values reflect stronger binding affinity between the ligand and the receptor [8]. The native ligand (MCO) and ajmaline shared key binding interactions with critical residues in the active site of the 1UZF protein, specifically HIS A:383 and GLU A:384. These interactions indicate that ajmaline may mimic the binding behavior of the native ligand, thereby targeting the angiotensin-converting enzyme in a similar manner.

Conclusion

Based on in silico study, ajmaline is potential for further exploration in the development of antihypertensive therapy.

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Author contribution

Conceptualization, AHS, ANR, WNA; Methodology, ANR, RRAA, DSP, HM, AFG, YSA, PAR, WNA; Investigation, WNA, AHS; Writing – Original Draft, ANR, RRAA, DSP, HM, AFG, YSA, PAR, AHS; Writing – Review & Editing, AHS.

Declaration of interest

None.

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