Molecular Docking studies of chemical constituents of Rauwolfia serpentina on hypertension

Abstract. Novel pharmaceutical molecules have been identified using computational approaches such as molecular docking, which are aimed at elucidating the molecular interactions of chemical constituents with key hypertensive targets. This study focused on investigating the anti-hypertensive effects of chemical constituents derived from Rauwolfia serpentina through computational simulations. The identified molecular complexes were analyzed to determine the most energetically favourable binding mode, three-dimensional structures, and to predict how a small molecule (ligand) interacts with a macromolecular target (usually a protein). To determine the interactions between the ligand and receptor, the computer analysis and prediction of interactions between two molecules, typically a small molecule (ligand) and a larger molecule (receptor), are performed using computational chemistry methods.

1 Introduction

Hypertension is still a prevalent cardiovascular disorder which remains a major global health concern. Rauwolfia serpentina, renowned for its therapeutic potential in managing hypertension, harbors a diverse array of bioactive compounds. This study aimed to elucidate the molecular interactions of chemical constituents of Rauwolfia serpentina with key hypertensive targets through molecular docking. The immediate and effective therapeutic output is gained through intake of medicinal plants. Because of their source, have been utilized in vivo studies, offering avenues for the development of novel therapeutic agents for hypertension management.

High blood pressure, a leading contributor to mortality and disability worldwide, has seen a significant rise in the past decade. The prevalence of hypertension, characterized by a systolic blood pressure greater than 140mm of Hg and the diastolic blood pressure greater than 90mm of Hg is considered as high blood pressure. But the investigative reports of Joint National Committee on prevention and detection and prevention of neurological diseases, these drug candidates are not reliable because they exhibit undesired side effects, drug interactions and stipulate high production cost that impacts the patient compliance.

In general, the immediate and effective therapeutic output is gained through intake of medicinal plants. Because of their source, have been utilized in vivo studies, offering avenues for the development of novel therapeutic agents for hypertension management. The immediate and effective therapeutic output is gained through intake of medicinal plants. Because of their source, have been utilized in vivo studies, offering avenues for the development of novel therapeutic agents for hypertension management.
created and explored. To compute binding affinity, algorithms consider shape complementarity, hydrogen bonding, and electrostatic interactions. Drug design and development benefit from molecular docking's virtual screening, lead optimisation, and ligand-receptor interaction insights. While it speeds up drug compound selection, experimental validation ensures reliability and accuracy. Molecular docking predicts and analyses molecular interactions, accelerating drug discovery.

L-name and Metoprolol, common synthetic antihypertensive medications, show strong binding affinity for elevated blood pressure. R. serpentine (Linn.) possesses antihypertensive properties that should be explored for hypertension molecular docking.

2 Material and methods

Twelve structures of chemical constituents of Rauwolfia serpentina i.e. Serpentinine, Deserpidine, Rescinnamidine, Reserpiline, Ajmalicine, Iso-ajmalicine, Serpentine, Alpha yohimbine, Yohimbine, Ajmaline, Sarpagine, Reserpine were collected from published literatures. The two-dimensional (2D) chemical structures of the ligands were sketched using ChemDraw Ultra 15.0, and the energy minimizations of the prepared ligands were carried out with Chem3D Ultra 15.0 and were saved in pdb format.

2.1 Chemical structures of Rauwolfia serpentina

![Chemical structures of Rauwolfia serpentina](image)

Alpha yohimbine  Iso-ajmaline  Yohimbine

Ajmalicine  Reserpine  Reserpiline

Rescinamidine  Sarpagine
2.2 Ligand preparation

In past studies focused on antihypertensive agents, 12 bioactive phytochemicals were specifically chosen for virtual screening and molecular docking against the Human Angiotensin Receptor (4ZUD). The 2D structures of these ligands were created using Chemdraw 15.0, and subsequently, Chem3D 15.0 was utilized to convert these structures into the Protein Data Bank (PDB) format \[15\]. For the purpose of conducting docking studies, AutoDock tools 1.5.7 were utilized to convert all designated ligands into PDBQT format. In the ligand preparation process, the procedure involved clicking on the ligand, selecting input, and then choosing the ligand through a dialog box, followed by molecule selection for AutoDock \[16\].

2.3 Target protein preparation

The crystal structure of the human angiotensin receptor, obtained from the RCSB Protein Data Bank (http://www.rcsb.org) and denoted by the PDB code 4ZUD, was utilized in this study. To identify protein structural inhibitors, the atomic coordinates of the PDB file were extracted. In order to eliminate potential interference from water molecules within the pocket region, autodock methods were employed to remove water molecules from the three-dimensional structure of the nucleoprotein. Polar hydrogen atoms were then added to the protein, and a docking pocket location was identified. The grid formation was specifically chosen, and using AutoDock Tools 1.5.7, the protein was designated as the macromolecule, resulting in the generation of a protein and ligand view. The grid box settings, important for locating the protein’s active site or docking area, were established, and the dimensions were displayed in the grid.txt file. Following the grid box configuration, the file was saved in the .pdbqt format using Autodock Tools 1.5.7 \[17\]. Image visualization of 4ZUD was performed using Discovery Studio 2021 which are shown in Fig 1.

2.4 Molecular docking analysis

An initial step involves creating a configuration file for protein-ligand docking, encompassing all necessary information for the docking process. AutoDock Tools 1.5.7 was employed to establish the grid box for the Human Angiotensin Receptor (4ZUD) with coordinates (X = -40.873, Y = 63.309, Z = 28.223) and dimensions of 36.00 x 22.00 x 26.00. The docking process, executed with AutoDock Vina in command mode, results in the generation of a log file and an output.pdbqt file upon completion. The output.pdbqt file contains ligand poses and an associated log file, presenting binding affinity values in kcal/mol. Predictions regarding the docking conformation of protein-ligand interactions are provided, with lower binding energies (more negative) indicating stronger binding affinities. Structure-based drug design involves the process of placing ligands into receptor binding sites and measuring their affinity for binding. AutoDock Vina is an open-source drug discovery tool that utilizes molecular docking and virtual screening. It is known for its multicore capabilities, high performance, accuracy, and user-friendly interface \[18\]. When the structure of the ligand-protein complex is known, the docking tool can be used to assess the parameters by comparing its ability to replicate the binding mode \[19\]. To determine the success of the docking process, the all-atom root mean square deviation (RMSD) between the predicted binding location and the actual observed position of the ligand should be less than 2Å°.
3 Results

In computational molecular studies, the interactions with their respective target macromolecules were investigated to evaluate ligand interactions. AutoDock Vina was employed to dock the standard antihypertensive medication metoprolol and L-NAME with the crystal structure of the Human Angiotensin Receptor (4ZUD). The resulting binding energies were determined to be -6.7 and -5.8 kcal/mol, respectively, which are shown in Table 1.

Furthermore, the binding pocket of Human Angiotensin Receptor (4ZUD) was systematically explored with various ligands, including Serpentinine, Deserpidine, Rescinnamidine, Reserpiline, Ajmalicine, Iso-Ajmalicine, Serpentine, Alpha yohimbine, Yohimbine, Ajmaline, Sarpagine, and Reserpine, using AutoDock Vina. The corresponding binding energies were measured as -10.5 kcal/mol, -10.0 kcal/mol, -9.9 kcal/mol, -8.8 kcal/mol, -8.7 kcal/mol, -8.6 kcal/mol, -8.3 kcal/mol, -8.2 kcal/mol, -7.9 kcal/mol, -7.7 kcal/mol, and -7.7 kcal/mol are presented in Table 1.

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Ligand</th>
<th>Docking score by Autodock vina (kcal/mol)</th>
</tr>
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<tbody>
<tr>
<td>1.</td>
<td>Serpentinine</td>
<td>-10.5</td>
</tr>
<tr>
<td>2.</td>
<td>Deserpidine</td>
<td>-10.0</td>
</tr>
<tr>
<td>3.</td>
<td>Rescinnamidine</td>
<td>-9.9</td>
</tr>
<tr>
<td>4.</td>
<td>Reserpiline</td>
<td>-8.8</td>
</tr>
<tr>
<td>5.</td>
<td>Ajmalicine</td>
<td>-8.7</td>
</tr>
<tr>
<td>6.</td>
<td>Iso-Ajmalicine</td>
<td>-8.6</td>
</tr>
<tr>
<td>7.</td>
<td>Serpentine</td>
<td>-8.6</td>
</tr>
<tr>
<td>8.</td>
<td>Alpha yohimbine</td>
<td>-8.3</td>
</tr>
<tr>
<td>9.</td>
<td>Yohimbine</td>
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</tr>
<tr>
<td>10.</td>
<td>Ajmaline</td>
<td>-7.9</td>
</tr>
<tr>
<td>11.</td>
<td>Reserpine</td>
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<td></td>
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<td></td>
<td>L-NAME</td>
<td>-5.8</td>
</tr>
<tr>
<td></td>
<td>Metoprolol</td>
<td>-6.7</td>
</tr>
</tbody>
</table>

4 Discussion

For Metoprolol with 4zud, the molecular interaction includes three Conventional H-bonds with THR A:260 at a bonding distance of 2.54 Å, GLN A:257 at the same 2.57 Å, and LYS A:199 at 2.47 Å. It also features one CH bond with GLN A:257 at 3.59 Å, one Pi-Pi shaped interaction with OLM A:1201, one Alkyl interaction with LEU A:112, and one Pi-alkyl interaction with TRP A:253. There are also two Van der Waals interactions with HIS A:256 and GLY A:203 [Fig.2 (A)].

The molecular interaction profile of L-NAME with 4zud involves four Conventional H-bonds: OLM A:1201 at a bonding distance of 2.15 Å, ARG A:167 at 2.22 Å, PHE A:182 at 1.90 Å, and CYS A:180 at 3.05 Å. Additionally, there are four Van der Waals interactions with MET A:284, ALA A:181, THR A:260, and GLN A:267 [Fig.2 (B)].

In comparison, the molecular interaction of Serpentinine with 4zud claims three Conventional H-bonds: GLN A:267 at 2.67 Å, ASP A:263 at 2.60 Å, and ARG A:23 at 2.84 Å. It also involves two CH bonds with PRO A:19 at 3.26 Å and TYR A:87 at 3.59 Å. Furthermore, there is one Pi-anion interaction with ASP A:281, two Pi-Pi T-shaped interactions with TYR A:184 and OLM A:1201, and one Pi-alkyl interaction with OLM A:1201. Numerous Van der Waals interactions include SER A:16, TYR A:92, PRO A:285, and ARG A:167 [Fig.3 (A)].

For Deserpidine, the molecular interaction claims six Conventional H-bond interactions: PHE A:182 at 1.93 Å, ARG A:167 at 2.61 Å, THR A:260 at 1.83 Å, OLM A:1201 at 2.71 Å, TYR A:184 at 2.59 Å, and GLN A:267 at 2.75 Å. It also includes one Pi-Donar H-bond with OLM A:1201 at 3.17 Å, one Pi-sigma interaction with LEU A:13, and one Pi-alkyl interaction with HIS A:256. Numerous Van der Waals interactions involve ILE A:288, ALA A:181, MET A:284, and ASP A:263 [Fig.3 (B)].

The molecular interaction of Rescinnamidine claims three conventional H-bonds: OLM A:1201 at 2.85 Å, PHE A:182 at 2.05 Å, and GLN A:267 at 2.85 Å. It also involves two CH bonds: GLY A:196 at 3.51 Å and ASP A:263 at 3.32 Å, as well as one Pi-sigma interaction with LEU A:13 and two Pi-alkyl interactions with HIS A:183 and ALA A:181. A Van der Waal interaction with ARG A:167 is also present [Fig.3 (C)].

Table 1
Furthermore, the experimental ligands more successfully met the requirements than Metoprolol and L-A.

A sufficient number of Van der Waals contacts predicts the solubility of all twelve bioactive ligands in lipid.

H and L are twenty (24) types of conventional H bonds that were studied in relation to ligand interaction were serpentinine, deserpidine, rescinnamidine, reserpiline, ajmalicine, iso-

The ligands that were studied in relation to ligand interaction were serpentinine, deserpidine, rescinnamidine, reserpiline, ajmalicine, iso-

1201. Three Van der Waals interactions with ALA A: 181, TYR A: 92, and CYS A: 180 are also present [Fig.3 (K)].

A: 1201, two Alkyl interactions with VAL A: 1201 at 2.48 Å. It also involves one C

The molecular interaction of Sarpagine claims two conventional H bonds with ALA A: 181 at 3.19 Å and PHE A: 182 at 3.39 Å. Additionally, there is one Unfavorable donor bond

For Reserpine, the molecular interaction claims one conventional H bond in their ligand contacts along with seven (7) different forms of c

The molecular interaction of Ajmaline claims one conventional H bond with ALA A: 181 at 3.33 Å, CYS A: 180 at 3.57 Å, TYR A: 87 at 3.65 Å, OLM A: 1201 at 3.47 Å, and

The molecular interaction of Yohimbine claims two conventional H bonds with ALA A: 181 at 4.27 Å, VAL A: 179 at 3.75 Å, and ILE A: 172 at 4.74 Å. It also involves one Pi

The molecular interaction of Reserpine claims two conventional H bonds with TYR A: 184 and one Pi

The molecular interaction of Alpha

The molecular interaction of Serpentine claims one conventional H bond with TYR A: 184 at 2.30 Å. It also includes one Pi

The molecular interaction of Ajmalicine claims one conventional H bond with TYR A: 87 at 3.57 Å and CYS A: 18 at 3.60 Å. It also involves one Alkyl interaction with

The molecular interaction of Reserpiline claims two conventional H bonds with TYR A: 184 and one Pi

The molecular interaction of Yohimbine claims two conventional H bonds with TYR A: 184 at 1.42 Å, one Pi

The molecular interaction of Arginine claims two conventional H bonds with ALA A: 21 at 3.19 Å, CYS A: 180 at 3.57 Å, TYR A: 87 at 3.65 Å, OLM A: 1201 at 3.47 Å, and

The molecular interaction of Metoprolol exhibits one C

For Iso-

The molecular interaction of Ajmalicine claims one conventional H bond (Carbon hydrogen bond) interactions, respectively. On the other hand, it was noted that metoprolol
the range of Conventional H bond distances of 2.52 Å, 2.60 Å, 2.84 Å, 1.93 Å, 2.61 Å, 1.83 Å, 2.71 Å, 2.59 Å, 2.75 Å, 2.85 Å, 2.05 Å, 2.85 Å, 2.37 Å, 2.71 Å, 1.99 Å, 2.11 Å, 2.44 Å, 2.30 Å, 2.03 Å, 2.40 Å, 2.82 Å, 2.48 Å predict good docking simulation outcomes [17].

All of the criteria for an antihypertensive medication are met by the compounds undergoing molecular docking research, along with additional possible hazard profiles.

Fig. 2: 2D interaction of standard drugs (A) Metoprolol (B) L-name
5 Conclusion

In this study, we investigated herbal remedies alongside FDA-approved medications for hypertension, identifying the R. serpentina (Linn.) plant as an optimal lead compound targeting the Human Angiotensin Receptor (PDB ID: 4ZUD). Through a comparative analysis, we determined that R. serpentina, particularly its bioactive phytoconstituent Serpentine, exhibited superior characteristics compared to commonly used medications such as L-name and metoprolol. Serpentine demonstrated a noteworthy binding affinity of -10.5 kcal/mol, establishing it as the most favorable molecular docking parameter among the tested compounds. Notably, all selected bioactive phytoconstituents for molecular docking exhibited higher binding affinities than prescription medications. The findings highlight R. serpentine (Linn.) as a potent antihypertensive agent, attributing its efficacy to substantial binding affinities in molecular interactions.

6 References

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