Molecular Docking studies of chemical constituents of Rauwolfia serpentina on hypertension

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Abstract. 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 derived from Rauwolfia serpentina with key hypertensive targets through molecular docking simulations. Utilizing computational tool, a comprehensive library of phytoconstituents obtained from Rauwolfia serpentina was constructed and subjected to molecular docking analyses against human angiotensin receptor (4ZUD) as target protein. The results revealed significant binding affinities between the chemical constituents of Rauwolfia serpentina and the active sites of these molecular targets. This study bridges the knowledge gap regarding the molecular mechanisms underlying the antihypertensive effects of Rauwolfia serpentina's constituents through computational simulations. The identified compounds exhibiting strong binding affinities and favorable interactions serve as promising candidates for further in vitro and in vivo studies, offering avenues for the development of novel therapeutic agents for hypertension management.

1 Introduction

High blood pressure, a leading contributor to mortality and disability worldwide, has seen a significant rise in the number of affected individuals in recent years. The prevalence of hypertension, characterized by a systolic blood pressure of at least 140 mmHg or a diastolic pressure of at least 90 mmHg, or being under medication, has doubled from 650 million to 1.3 billion [1]. Hypertension stands out as a critical risk factor for cardiovascular diseases such as stroke, heart attack, heart failure, and aneurysm. Effectively managing blood pressure is paramount to preserving health and reducing the risk of encountering these potentially fatal conditions [2].In general, the 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 detection and prevention of high blood pressure [3] revealed that a 20mm of Hg increase in the systolic blood pressure and a 10mm of Hg increase in the diastolic blood pressure is considered as elevated blood pressure and should be urged for prompt treatment. The immediate and effective therapeutic output is gained through intake of miscellaneous pharmacological drug molecules categorized as beta blockers, calcium channel blockers, ACE inhibitors, alpha blockers, and diuretics. In spite of their therapeutic demand, these drug candidates are not reliable because they exhibit undesired side effects, drug interactions and stipulate huge production cost that impacts the patient compliance [4].

Plant based medicine, regardless of their source, have been utilized as medications for decades and are helpful to human and animal health [5].Because of minimal side effects, natural medicinal herbs find extensive usage in the treatment of neurological disorders. The use of plant-based methods has become more important in treating hypertension. Incorporating phytochemicals from plants into hypertension treatment regimens provides a natural and possibly efficacious approach to regulating blood pressure [6].Because of their high bioactivity, studies investigating the anti- hypertensive effects of these botanical components have shown positive findings. [7]
Rauwolfia serpentina (Linn.) Benth.ex Kurz is a medicinal plant belongs to the family of *Apocynaceae* [8] found in abundance in India, particularly in the wet damp forest areas. It is commonly known as *Sarpagandha*. Generally plant root is used as primarily and also having numerous therapeutic activities when compared with leaves and stem. Sarpagandha is administered as first category drug for antihypertensive disorder. It has also proven that having anti-venom, anti-bacterial, anti-diabetic, anti-inflammatory, anti-diarrhea activities [9]. The potent active chemical constituents in sarpagandha contains Serpentinine, Deserpidine, Rescinnamidine, Reserpiline, Ajmalicine, Iso-ajmalicine, Serpentine, Alpha yohimbine, Yohimbine, Ajmaline, Sarpagine, Reserpine [10].

Novel pharmaceutical molecules have been identified using computational approaches such as molecular docking. The computer analysis and prediction of interactions between two molecules, typically a small ligand and a larger receptor, is known as molecular docking [11]. Drug discovery and structural biology employ molecular docking to predict how a small molecule (ligand) interacts with a macromolecular target (usually a protein). To determine the most energetically favourable binding mode, three-dimensional structures of the ligand and receptor are

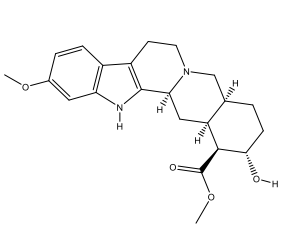
created and explored. To compute binding affinity, algorithms consider shape complementarity, hydrogen bonding, and electrostatic interactions [12]. Drug design and development benefit from molecular docking's virtual screening, lead optimisation, and ligand-receptor interaction insights. While it speeds up drug compound selection, experimental validation ensures reliability and accuracy. Molecular docking predicts and analyses molecular interactions, accelerating drug discovery [13].

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.

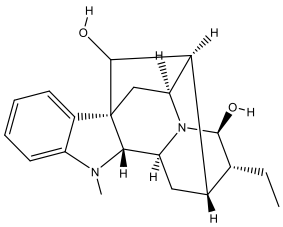
2 Material and methods

Twelve structures of chemical constituents of *R.serpentina* i.e. Serpentinine, Deserpidine, Rescinnamidine, Reserpiline, Ajmalicine, Iso-ajmalicine, Serpentine, Alpha yohimbine, Yohimbine, Ajmaline, Sarpagine, Reserpine were collected from published literatures [14]. 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 serprntina*



Alpha yohimbine



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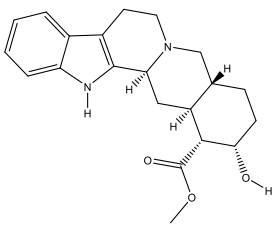

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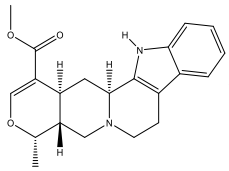
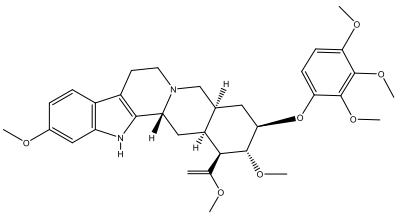
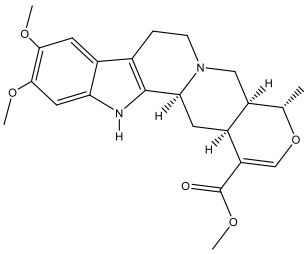


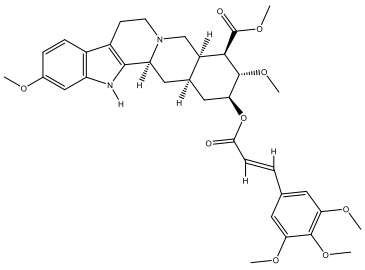
Ajmalicine



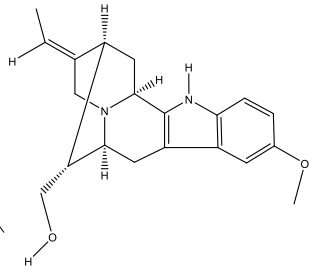
Reserpine



Reserpiline



Rescinnamidine



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**.

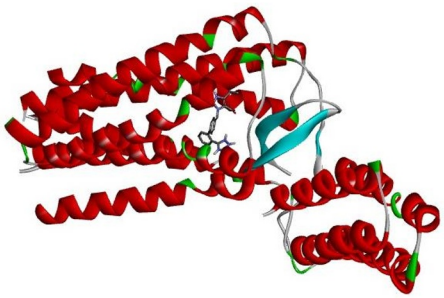


Fig.1 Human Angiotensin Receptor PDB ID: 4ZUD

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 2Á°.

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 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.1. Consensus docking affinity score of bioactive ligands against Human Angiotensin Receptor (4ZUD) target protein

S. No.	Ligand	Docking score by Autodock vina (kcal/mol)
1.	Serpentinine	-10.5
2.	Deserpidine	-10.0
3.	Rescinnamidine	-9.9
4.	Reserpilin	-8.8
5.	Ajmalicine	-8.7
6.	Iso-ajmaline	-8.6
7.	Serpentine	-8.6
8.	Alpha-yohimbine	-8.3
9.	Yohimbine	-8.2
10.	Ajmaline	-7.9
11.	Reserpine	-7.7
12.	Sarpagine	-7.7
13.	L-name	-5.8
14.	Metoprolol	-6.7

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 C-H 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 C-H 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 C-H 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)].

The molecular interaction of Reserpiline claims two conventional H-bonds: THR A: 260 with 2.50 Å and OLM A: 1201 with 2.37 Å. It also features one C-H bond with TYR A: 184 at 3.68 Å, one Pi-sigma interaction with MET A: 284, and one alkyl interaction with VAL A: 264. Two Pi-alkyl interactions with MET A: 284 and OLM A: 1201 and several Van der Waals interactions involving ARG A: 167, TYR A: 87, TYR A:92, ILE A:288, and HIS A:256 are present [Fig. 3(D)].

The molecular interaction of Ajmalicine claims one conventional H-bond with PHE A: 182 at 2.71 Å and two C-H bonds with ASP A: 263 at 3.52 Å and OLM A: 1201 at 3.49 Å. It also includes one Pi-Pi T-shaped interaction with TYR A: 184 and one Pi-alkyl interaction with LEU A: 13, along with three Van der Waals interactions involving ARG A: 167, GLN A: 267, and ALA A: 181 [Fig.3(E)].

For Iso-ajamaline, the molecular interaction claims one conventional H-bond with TYR A: 87 at 1.99 Å and three C-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-alkyl interaction with ARG A: 23 and several other Van der Waals interactions with TYR A: 92, OLM A: 1201, and ARG A: 167 [Fig.3(F)].

The molecular interaction of Serpentine claims one conventional H-bond with PHE A: 182 at 2.11 Å and five C-H bonds 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 ASP A: 263 at 3.47 Å. It also features one Pi-sigma interaction with LEU A: 13, one Pi-PI T-shaped interaction with TYR A: 184, one Pi-alkyl interaction with ALA A: 181, and numerous Van der Waals interactions with ARG A: 167, GLN A: 267, and VAL A: 179 [Fig.3(G)].

The molecular interaction of Alpha-yohimbine claims one conventional H-bond with GLN A:267 at 2.44 Å and two C-H bonds with TYR A: 87 at 3.57 Å and CYS A: 18 at 3.60 Å. It also involves one Alkyl interaction with VAL A: 179 and one Pi-alkyl interaction with TYR A: 92, along with several Van der Waals interactions with ARG A: 23, ALA A: 181, OLM A: 1201, ILE A: 172, ALA A: 21, and ASP A: 263 [Fig. 3(H)].

The molecular interaction of Yohimbine claims two conventional H-bonds with PHE A: 182 at 2.03 Å and TYR A: 184 at 2.30 Å. It also includes one Pi-sigma interaction with LEU A: 13 and one Pi-alkyl interaction with LEU A: 13, along with one Van der Waal interaction with ALA A: 181 [Fig.3 (I)].

The molecular interaction of Ajmaline claims one conventional H-bond with ASP A: 281 at 2.81 Å and one Pi-sigma interaction with VAL A: 179. It also features two Alkyl interactions with MET A: 284 and OLM A: 1201, one Pi-alkyl interaction with ILE A: 172, and three Van der Waals interactions with TYR A: 92, PRO A: 285, and ALA A: 181 [Fig.3 (J)].

For Reserpine, the molecular interaction claims one conventional H-bond with SER A: 16 at 2.44 Å and two C-H bonds with ALA A: 21 at 3.19 Å and PHE A: 182 at 3.39 Å. Additionally, there is one Unfavorable donor bond with TYR A: 184 at 1.42 Å, one Pi-anion interaction with ASP A: 263, one Pi-cation interaction with ARG A: 167, and one Pi-sigma interaction with OLM A: 1201. Three Alkyl interactions with VAL A: 179, ARG A: 23, and ILE A: 172 and two Pi-alkyl interactions with TYR A: 92 and OLM A:1201, along with numerous other Van der Waals interactions involving ILE A:288, PRO A: 19, GLN A: 267, and ALA A: 181 [Fig.3 (K)].

The molecular interaction of Sarpagine claims two conventional H-bonds with ARG A: 167 at 2.82 Å and OLM A: 1201 at 2.48 Å. It also involves one C-H bond with TYR A: 87 at 3.52 Å, one Pi-anion interaction with OLM A: 1201, two Alkyl interactions with VAL A: 179 and ILE A: 172, and one Pi-alkyl interaction with OLM A: 1201. Three Van der Waals interactions with ALA A: 181, TYR A: 92, and CYS A: 180 are also present [Fig.3 (L)].

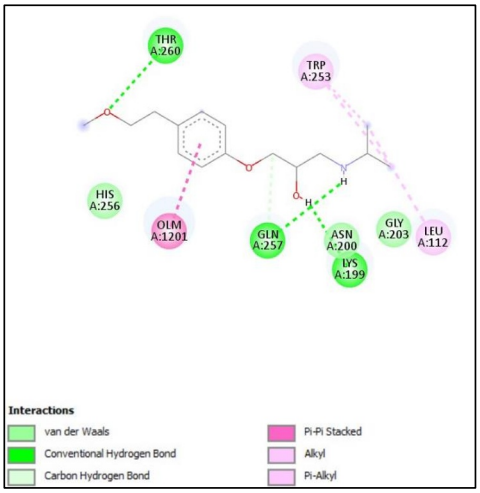
The ligands that were studied in relation to ligand interaction were serpentinine, deserpidine, rescinnamidine, reserpiline, ajmalicine, iso-ajmalicine, serpentine, alpha yohimbine, yohimbine, ajmaline, reserpine and sarpagine. These ligands exhibited both conventional H-Bond and C-H bond interactions with amino acid residues, including twenty (24) types of conventional H-Bond interactions and seventeen (17) types of C-H bond interactions. Deserpidine and serpentine are the ligands that exhibit the highest number of conventional H-bond interactions and C-H bond (Carbon hydrogen bond) interactions, respectively. On the other hand, it was noted that metoprolol and L-name exhibited one C-H bond in their ligand contacts along with seven (7) different forms of conventional H-Bond interactions.

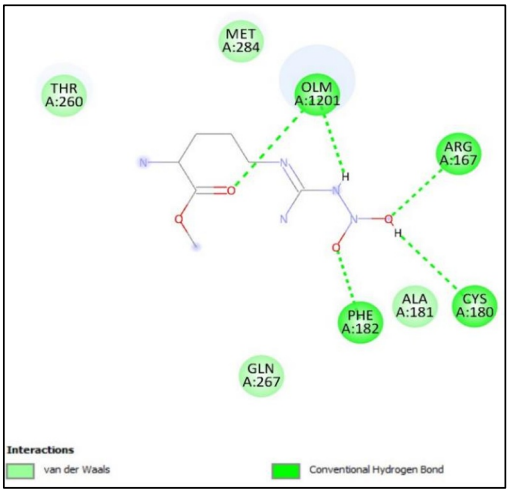
A sufficient number of Van der Waals contacts predicts the solubility of all twelve bioactive ligands in lipid. Furthermore, the experimental ligands more successfully met the requirements than Metoprolol and L-name, and

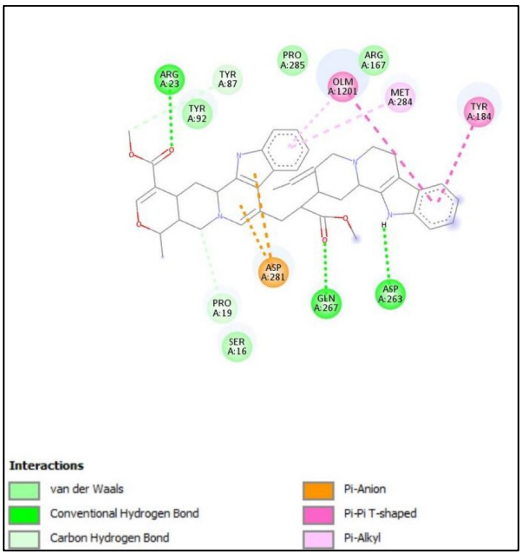
the range of Conventional-H bond distances of 2.52 Å, 2.60 Å, 2.84 Å, 1.93 Å, 2.61 Å, 1.83 Å, 2.71 Å, 2.59 Å, 2.75 Å, 2.85 Å, 2.05 Å, 2.85 Å, 2.37 Å, 2.71 Å, 1.99 Å, 2.11 Å, 2.44 Å, 2.30 Å, 2.03 Å, 2.40 Å, 2.82 Å, 2.48 Å predict good docking simulation outcomes [17]. All of the criteria for an antihypertensive medication are met by the compounds undergoing molecular docking research, along with additional possible hazard profiles.

(A) **(B)**

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

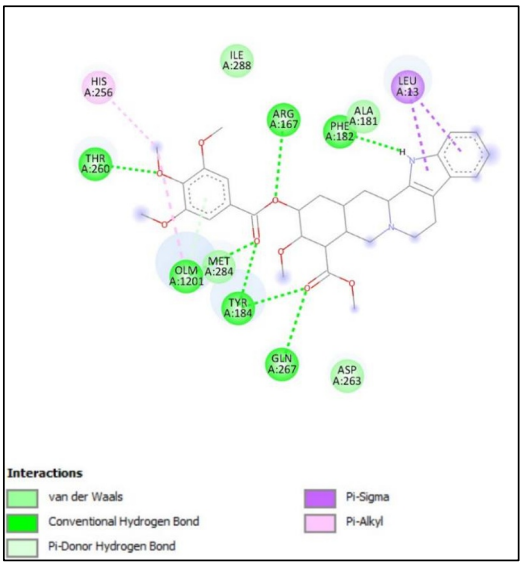


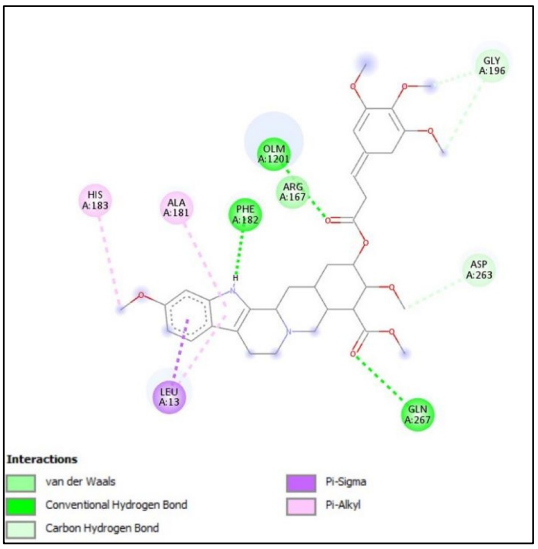




(A)

(B)

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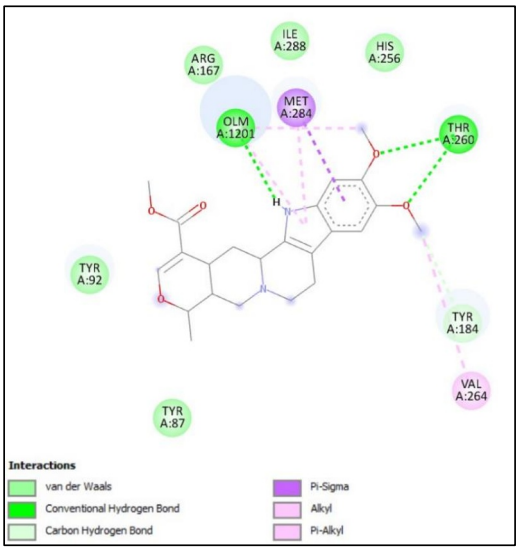
Carbon Hydrogen Bond
Pi-Sigma
Pi-Alkyl

(C)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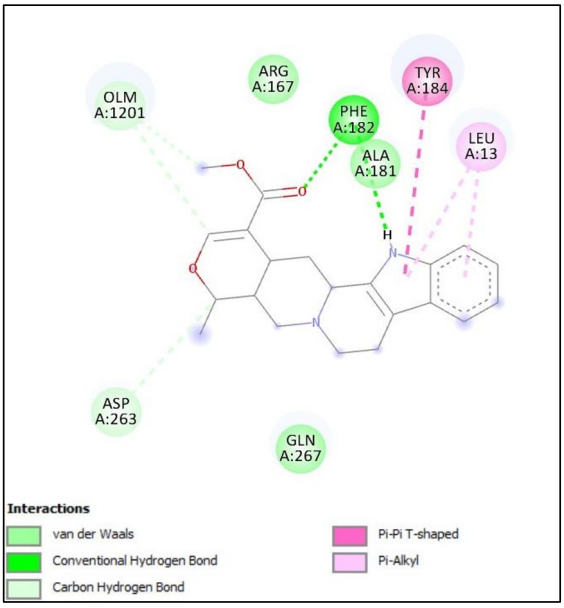
Pi-Sigma
Alkyl
Pi-Alkyl

(D)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van der Waals
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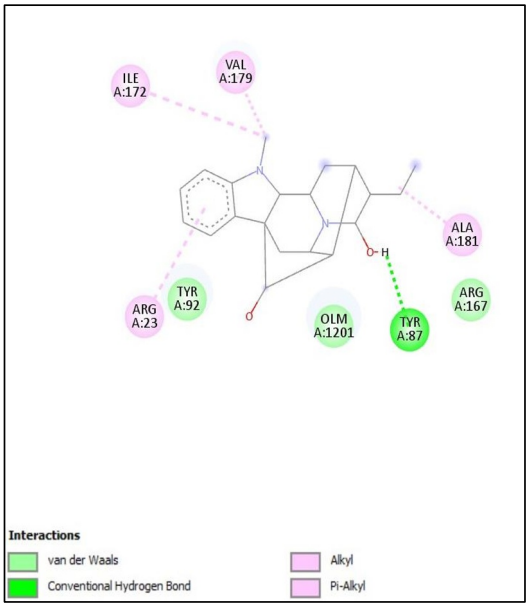
Carbon Hydrogen Bond
Pi-Pi T-shaped
Pi-Alkyl

(E)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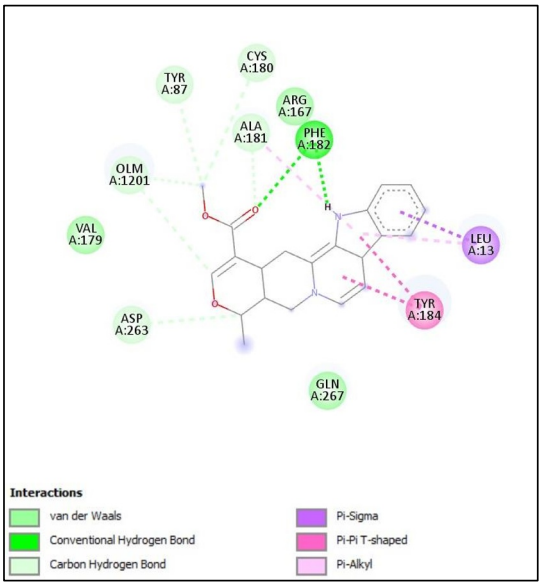
van der Waals
Conventional Hydrogen Bond
Alkyl
Pi-Alkyl

(F)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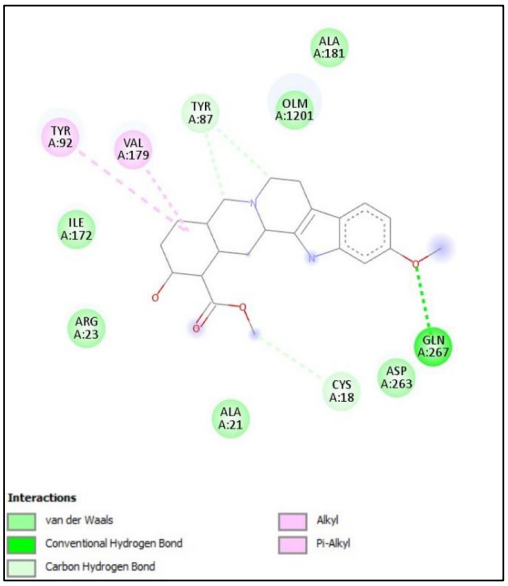
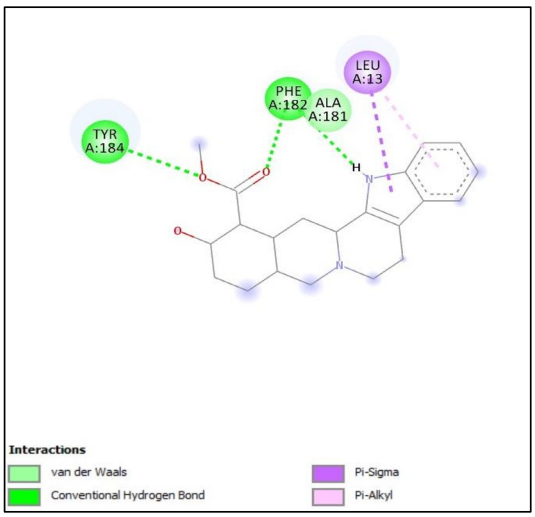
ASP A:263
GLN A:267
Interactions
van der Waals
Conventional Hydrogen Bond
Carbon Hydrogen Bond
Pi-Sigma
Pi-Pi T-shaped
Pi-Alkyl

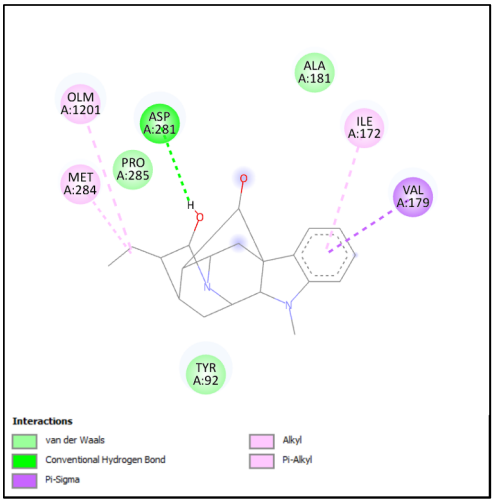
(G)


ALA A:181
TYR A:87
OLM A:1201
TYR A:92
VAL A:179
ILE A:172
ARG A:23
GLN A:267
ASP A:263
CYS A:18
ALA A:21
Interactions
van der Waals
Conventional Hydrogen Bond
Carbon Hydrogen Bond
Alkyl
Pi-Alkyl

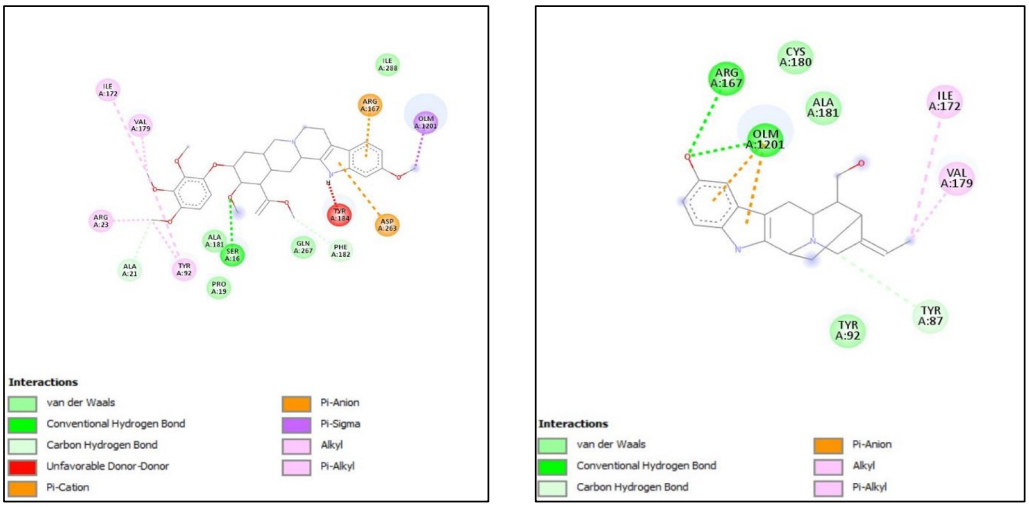
(H)


LEU A:13
PHE A:182
ALA A:181
TYR A:184
Interactions
van der Waals
Conventional Hydrogen Bond
Pi-Sigma
Pi-Alkyl

(I)


ALA A:181
OLM A:1201
ASP A:281
ILE A:172
PRO A:285
MET A:284
VAL A:179
TYR A:92
Interactions
van der Waals
Conventional Hydrogen Bond
Pi-Sigma
Alkyl
Pi-Alkyl

(J)



(K) **(L)**

Fig. 3 2 D interactions (A) Serpentinine,(B) Deserpidine, (C) Rescinnamidine,(D) Reserpiline, (E) Ajmalicine, (F) Iso-ajmalicine, (G) Serpentine, (H) Alpha yohimbine, (I) Yohimbine, (J) Ajmaline, (K) Reserpine and (L) Sarpagine

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.

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