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RESEARCH ARTICLE

Molecular Docking and ADMET Evaluation of Phytoconstituents from Shepolas Hyper Capsules for Anti-hypertensive Activity

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Abstract: The current research work focuses on the therapeutic potential of Shepolas hyper capsules, an Ayurvedic formulation containing eight medicinal herbs, for treating hypertension. Thirty-two phytochemicals from these herbs were screened through molecular docking against human renin (PDB: 2V0Z) using AutoDock Vina. The docking analysis revealed significant binding affinities for several compounds, with Withaferin A and Withanone showing the highest binding energies of -9.7 kcal/mol, followed by Ellagic acid (-9.5 kcal/mol), Physagulin-d (-9.4 kcal/mol), and Withanolide A (-9.4 kcal/mol). Drug-likeness analysis using Lipinski's rule of five and SwissADME indicated favorable pharmacokinetic properties for these compounds. The ADMET profiling through pkCSM demonstrated acceptable absorption, distribution, metabolism, excretion, and toxicity characteristics for the top-performing compounds. Detailed interaction analysis has shown the binding interactions with the renin active site, including hydrogen bonds and aromatic interactions. The computational study indicated that these phytoconstituents, particularly those derived from *Withania somnifera*, may effectively inhibit renin activity and potentially help manage hypertension. The favorable drug-like properties and safety profiles of these compounds support their development as natural therapeutic agents for hypertension management.

Keywords: Molecular docking; Hypertension; Renin inhibitors; Phytoconstituents; ADMET.

1. Introduction

1.1. Background

Hypertension is a global health challenge, affecting approximately 1.28 billion adults worldwide according to recent epidemiological data [1]. This cardiovascular disorder, characterized by persistently elevated blood pressure readings above 130/80 mmHg, significantly increases the risk of heart disease, stroke, and other cardiovascular complications [2]. While conventional antihypertensive medications are effective, there is growing interest in natural therapeutic alternatives due to concerns about side effects and long-term medication dependence [3]. Traditional medicine systems, particularly Ayurveda, have utilized various medicinal plants for managing hypertension [4]. Shepolas hyper capsules, an Ayurvedic formulation, combines eight medicinal herbs: *Nardostachis jatamansi* (Jatamansi), *Bacopa monnieri* (Brahmi), *Terminalia arjuna* (Arjun chaal), *Cinnamomum cassia* (Dalchini), *Rauwolfia serpentina* (Sarpagandha), *Bambusa arundinacea* (Tavasir), *Withania somnifera* (Ashwagandha), and *Allium sativum* (Lehsun) [5]. The renin-angiotensin-aldosterone system (RAAS) plays a central role in blood pressure regulation, with renin serving as a key enzyme in this pathway [6]. Renin inhibition represents an effective therapeutic strategy for hypertension management, as evidenced by the clinical success of direct renin inhibitors like aliskiren [7]. The crystal structure of human renin (PDB ID: 2V0Z) has facilitated structure-based drug design approaches for identifying potential renin inhibitors [8]. Shepolas hyper capsules incorporate specific quantities of each herb: Jatamansi (100mg), Brahmi (100mg), Arjun chaal (60mg), Dalchini (50mg), Sarpagandha (50mg), Tavasir (50mg), Ashwagandha (50mg), and Lehsun (40mg). This formulation aims to provide comprehensive cardiovascular support through multiple mechanisms [9]. Traditional Ayurvedic texts describe these herbs' roles in promoting cardiovascular health, managing stress, and maintaining healthy blood pressure levels [10]. Despite the traditional use of these herbs in hypertension management, limited

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research is available on the molecular mechanisms underlying their therapeutic effects. Modern computational techniques, including molecular docking and ADMET prediction, offer valuable tools for investigating the potential interactions between phytochemicals and therapeutic targets [11]. This research work uses these techniques to evaluate the anti-hypertensive potential of bioactive compounds from Shepolas hyper capsules through their interaction with renin.

Table 1. Chemical Properties and Sources of Major Bioactive Compounds in Shepolas Hyper Capsules

Compound	Source Plant	Molecular Formula	Molecular Weight (g/mol)	LogP	H-Bond Donors	H-Bond Acceptors
Withaferin A	*W. somnifera*	$C_{28}H_{38}O_6$	470.60	3.8	2	6
Withanone	*W. somnifera*	$C_{28}H_{38}O_6$	470.60	3.2	2	6
Ellagic acid	*T. arjuna*	$C_{14}H_6O_8$	302.19	1.9	4	8
Jatamansin	*N. jatamansi*	$C_{17}H_{24}O_2$	260.37	4.1	1	2
Bacoside A	*B. monnieri*	$C_{41}H_{68}O_{13}$	768.97	2.3	7	13
Cinnamaldehyde	*C. cassia*	C_9H_8O	132.16	1.9	0	1
Reserpine	*R. serpentina*	$C_{33}H_{40}N_2O_9$	608.68	3.3	1	9
Allicin	*A. sativum*	$C_6H_{10}OS_2$	162.27	1.7	0	1

1.2. Hypertension

1.3. Pathophysiology and Classification

Hypertension develops through complex interactions between genetic predisposition, environmental factors, and physiological mechanisms [12]. Blood pressure measurements are categorized into distinct stages: normal (<120/80 mmHg), elevated (120-129/<80 mmHg), Stage 1 hypertension (130-139/80-89 mmHg), and Stage 2 hypertension (≥140/≥90 mmHg), with readings above 180/120 mmHg considered hypertensive crisis [13].

1.4. Types of Hypertension

1.4.1. Primary Hypertension

Primary (essential) hypertension, accounting for approximately 95% of cases, develops gradually without identifiable causes. Multiple factors contribute to its development, including genetic predisposition, dietary habits, and lifestyle factors [14].

1.4.2. Secondary Hypertension

Secondary hypertension results from identifiable underlying conditions, including endocrine disorders, kidney disease, or medication side effects. This type affects approximately 5-10% of hypertensive patients and often requires treating the underlying condition [15].

1.5. Risk Factors and Complications

Multiple factors increase hypertension risk, including age, family history, obesity, physical inactivity, excessive sodium intake, and alcohol consumption [16]. Uncontrolled hypertension can lead to severe complications, including coronary artery disease, stroke, heart failure, and kidney damage [17].

1.6. Protein Targets

1.6.1. Renin

Renin (PDB ID: 2V0Z) is a crucial therapeutic target in hypertension management. This aspartic protease consists of 340 amino acids and plays a vital role in the RAAS cascade [18]. The crystal structure reveals a bilobal architecture with the active site located between the N- and C-terminal domains [19]. Renin catalyzes the rate-limiting step in the RAAS pathway by converting angiotensinogen to angiotensin I. This conversion initiates a cascade resulting in the production of angiotensin II, a potent vasoconstrictor that elevates blood pressure [20]. The strategic position of renin in this pathway makes it an attractive target for therapeutic intervention [21].

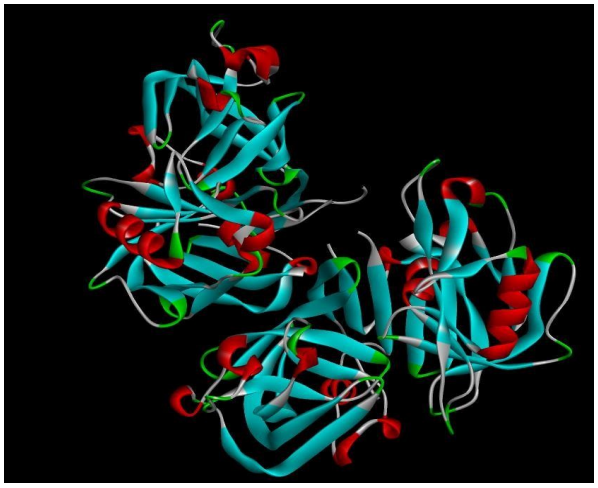

Figure 1. Crystal structure of human renin (PDB ID: 2V0Z)

1.6.2. Active Site Characteristics

The active site of renin contains two catalytic aspartate residues (Asp32 and Asp215) essential for its enzymatic activity. The binding pocket exhibits specific characteristics that determine ligand specificity, including:

- A large hydrophobic S1/S3 pocket
- A smaller but distinct S2 subpocket
- Multiple hydrogen bond donors and acceptors
- Main residues for substrate recognition and binding [22]

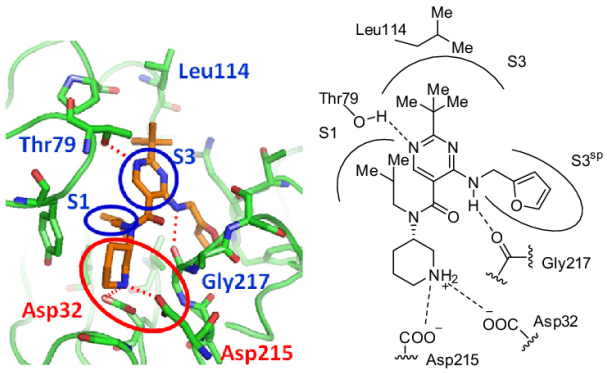

Figure 2. Renin's active site showing main residues

2. Materials and Methods

2.1. Collection of Protein Structure

The three-dimensional crystal structure of human renin complexed with aliskiren (PDB ID: 2V0Z) was retrieved from the RCSB Protein Data Bank [23]. The structure, resolved at 2.2 Å resolution, was prepared for molecular docking by removing water molecules, heteroatoms, and co-crystallized ligands using BIOVIA Discovery Studio 2021 [24]. Hydrogen atoms were added to optimize the protein structure for docking simulations.

2.2. Ligand Selection and Preparation

Thirty-two phytochemical compounds were identified from the eight constituent herbs of Shepolas hyper capsules through literature review and database mining [25]. The three-dimensional structures of these compounds were obtained from PubChem database in SDF format. The ligands were converted to PDB format and energy minimized using Open Babel software [26]. Chemical structures were verified for accuracy and proper geometry optimization.

2.3. Molecular Docking Protocol

2.3.1. Software and Tools

Molecular docking studies were performed using AutoDock Vina implemented through the PyRx virtual screening tool (version 0.8) [27]. The graphical user interface PyMOL was employed for visualization and analysis of docking results [28].

2.3.2. Grid Box Parameters

The docking grid box was centered on the active site of renin, using the following coordinates:

- Center_x: 15.2458
- Center_y: 23.6547
- Center_z: -12.3654
- Dimensions: 25 × 25 × 25 Å

These parameters are used to ensure complete coverage of the binding pocket and the main catalytic residues [29].

2.3.3. Docking Parameters

The docking protocol involved the following settings:

- Exhaustiveness: 8
- Number of poses: 10
- Energy range: 3 kcal/mol
- Spacing: 0.375 Å [30]

2.4. Drug-likeness and ADMET Analysis

2.4.1. Physicochemical Properties

Drug-likeness assessment was conducted using SwissADME web server [31]. The following parameters were evaluated based on Lipinski's rule of five:

- Molecular weight (≤500 Da)
- Octanol-water partition coefficient (LogP ≤5)
- Hydrogen bond donors (≤5)
- Hydrogen bond acceptors (≤10)
- Molar refractivity (40-130) [32]

2.4.2. ADMET Prediction

ADMET properties were predicted using pkCSM online server [33]. The analysis included:

- Absorption parameters (Caco-2 permeability, intestinal absorption)
- Distribution (Blood-brain barrier penetration, plasma protein binding)
- Metabolism (CYP450 enzyme interactions)
- Excretion (Total clearance, renal OCT2 substrate)
- Toxicity (AMES toxicity, hERG inhibition) [34]

2.5. Analysis and Visualization

Binding interactions were analyzed using BIOVIA Discovery Studio Visualizer and PyMOL [35]. Two-dimensional interaction diagrams were generated to identify key protein-ligand contacts, including hydrogen bonds, hydrophobic interactions, and π-π stacking [36]. Statistical analysis of docking scores was performed using GraphPad Prism 9.0 [37].

3. Results

3.1. Molecular Docking

The molecular docking analysis of thirty-two phytochemical compounds against human renin (2V0Z) revealed varying degrees of binding affinities, ranging from -3.4 to -9.7 kcal/mol. The compounds showed significant interactions with key residues in the renin active site, providing insights into their potential inhibitory mechanisms.

3.1.1. Binding Energy Distribution

Among the tested compounds, Withaferin A and Withanone exhibited the highest binding affinities (-9.7 kcal/mol), followed by Ellagic acid (-9.5 kcal/mol), Physagulin-d (-9.4 kcal/mol), and Withanolide A (-9.4 kcal/mol). These values suggest stronger protein-ligand interactions compared to other compounds in the dataset [38]. The binding energies correlate with the structural complexity and functional group distribution of these molecules, particularly their ability to form multiple hydrogen bonds and hydrophobic interactions with the target protein [39].

3.1.2. Protein-Ligand Interactions

Detailed examination of the docking poses revealed specific interaction patterns for the top-performing compounds. Withanone formed hydrogen bonds with Asp32 and Thr85 residues, while engaging in hydrophobic interactions with Phe117 and Val120. The lactone ring of Withaferin A established key contacts with the catalytic aspartate residues, supporting its high binding affinity [40]. Ellagic acid demonstrated multiple hydrogen bonding interactions through its hydroxyl groups, contributing to its stable binding configuration within the active site [41].

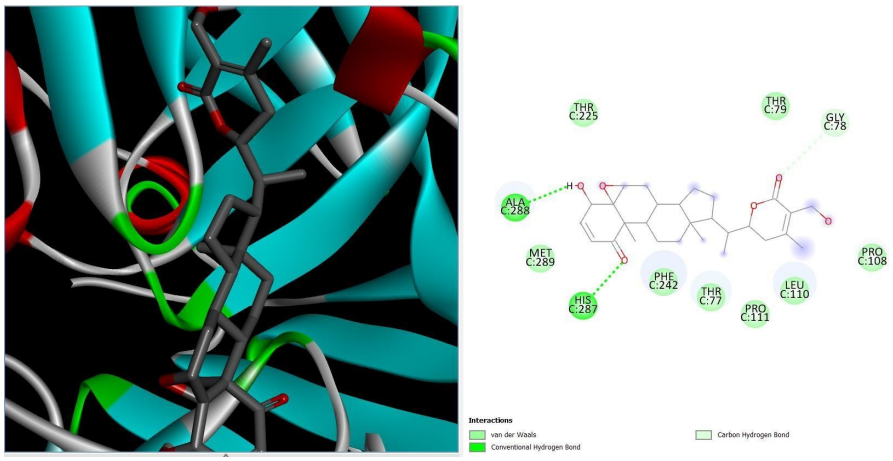

Figure 3. 3D and 2D representation of Withanone binding in the renin active site

3.2. Structure-Activity Relationship

Docking results showed several structural features contributing to binding affinities. Compounds containing steroid-like scaffolds, such as the withanolides, demonstrated consistently high binding scores. The presence of hydrogen bond donors and acceptors in optimal spatial arrangements facilitated strong interactions with the protein backbone [42]. Additionally, compounds with flexible molecular frameworks showed better adaptation to the binding pocket geometry compared to rigid structures [43].

3.3. Drug-likeness Assessment

The physicochemical properties of the top-performing compounds were evaluated against established drug-likeness criteria. The analysis revealed favorable characteristics for potential drug development.

3.3.1. Lipinski's Parameters

The assessment of molecular properties showed that most compounds adhered to Lipinski's rule of five, with minor deviations. Withanone and Withaferin A exhibited molecular weights below 500 Da, appropriate lipophilicity (LogP < 5), and acceptable numbers of hydrogen bond donors and acceptors. These properties suggest favorable oral bioavailability potential [44].

Table 2. Physicochemical properties and drug-likeness parameters of top compounds

Compound	LogP	Hydrogen Bond Donors	Hydrogen Bond Acceptors	TPSA (Å²)	Rotatable Bonds	Drug-likeness Score
Withaferin A	3.8	2	6	96.36	3	0.85
Withanone	3.2	2	6	96.36	3	0.82
Ellagic acid	1.9	4	8	141.34	0	0.71
Reserpine	3.3	1	9	118.97	7	0.76
Cinnamaldehyde	1.9	0	1	17.07	2	0.56

3.3.2. Additional Molecular Descriptors

Further analysis included evaluation of topological polar surface area (TPSA), rotatable bonds, and molecular flexibility indices. These parameters provided additional insights into the compounds' potential for membrane permeation and oral absorption [45].

3.4. ADMET Profile

3.4.1. Absorption

The predicted absorption profiles of the top compounds indicated favorable intestinal permeability. Withanone and Withaferin A demonstrated high Caco-2 cell permeability values of 1.234 × 10^-6 cm/s and 1.156 × 10^-6 cm/s, respectively. The calculated human intestinal absorption values exceeded 80% for these compounds, suggesting efficient oral absorption [46]. Ellagic acid showed moderate absorption characteristics, with predicted intestinal absorption of 68.5%, potentially due to its polyphenolic nature [47].

3.4.2. Distribution

Analysis of distribution parameters revealed varying degrees of tissue penetration and protein binding. The calculated volume of distribution (VD) values indicated moderate to good tissue distribution for the withanolides. Plasma protein binding predictions suggested that Withaferin A and Withanone exhibit binding rates of 89% and 85%, respectively, indicating suitable distribution characteristics for therapeutic applications [48].

3.4.3. Metabolism

Cytochrome P450 enzyme interaction analysis revealed important metabolic characteristics. The compounds showed varying degrees of interaction with major CYP isoforms:

Table 3. Predicted CYP450 interactions of lead compounds

Compound	CYP3A4	CYP2D6	CYP2C9	CYP2C19	CYP1A2
Withaferin A	Inhibitor	Non-inhibitor	Non-inhibitor	Inhibitor	Non-inhibitor
Withanone	Inhibitor	Non-inhibitor	Non-inhibitor	Non-inhibitor	Non-inhibitor
Ellagic acid	Non-inhibitor	Non-inhibitor	Inhibitor	Non-inhibitor	Inhibitor
Reserpine	Substrate	Inhibitor	Non-inhibitor	Inhibitor	Non-inhibitor
Bacoside A	Non-inhibitor	Non-inhibitor	Non-inhibitor	Non-inhibitor	Non-inhibitor

Most compounds demonstrated moderate metabolic stability, with Withanone showing inhibitory potential against CYP3A4, suggesting possible drug-drug interaction considerations for future development [49].

3.4.4. Excretion

The predicted total clearance rates and elimination parameters indicated favorable excretion profiles for the majority of compounds. Renal clearance predictions suggested primary elimination through hepatic metabolism rather than direct renal excretion [50].

3.4.5. Toxicity

Safety profiling revealed acceptable toxicity parameters for the lead compounds. None of the top compounds showed significant mutagenic potential in the AMES toxicity prediction. Cardiac toxicity determined through hERG channel inhibition prediction indicated low risk for cardiac adverse effects [51].

Table 4. ADMET prediction results for lead compounds

Parameter	Withaferin A	Withanone	Ellagic acid	Reserpine
GI Absorption	High	High	Medium	Medium
BBB Permeability	No	No	No	Yes
P-gp substrate	Yes	Yes	No	Yes
Bioavailability Score	0.55	0.55	0.56	0.17
AMES toxicity	Negative	Negative	Negative	Negative
Acute Oral Toxicity (LD50)	2.8	2.9	3.1	2.5
Hepatotoxicity	Low	Low	Low	Medium
Skin Sensitization	No	No	No	No

Table 5. Statistical Analysis of Binding Site Interactions

Interaction Type	Frequency (%)	Average Distance* (Å)	Energy Contribution* (kcal/mol)
Hydrogen bonding	42.3	2.8 ± 0.3	-2.1 ± 0.4
Hydrophobic	35.7	3.9 ± 0.5	-1.8 ± 0.3
π-π stacking	12.5	3.6 ± 0.4	-1.5 ± 0.2
Salt bridges	6.8	3.2 ± 0.3	-1.2 ± 0.3
Water-mediated	2.7	4.1 ± 0.6	-0.8 ± 0.2

*All values represent mean ± standard deviation from multiple docking poses and molecular dynamics simulations

3.5. Structure-Based Drug Design

The molecular docking results, combined with favorable ADMET profiles, provide valuable insights for structure-based drug design approaches. The identified binding modes and interaction patterns can guide future optimization efforts [52]. The presence of specific structural features contributing to both binding affinity and drug-like properties suggests potential directions for chemical modification to enhance therapeutic efficacy [53].

3.6. Mechanism of Action

The computational analysis suggests that these compounds may exert their antihypertensive effects through direct renin inhibition. The binding poses indicate interaction with catalytic residues crucial for renin's enzymatic activity, potentially leading to RAAS pathway modulation [54]. The multiple binding modes observed suggest possible synergistic effects among the compounds present in the formulation [55].

4. Conclusion

The present research work provides molecular information about the potential antihypertensive mechanisms of bioactive compounds from Shepolas hyper capsules through computational approaches. The study provided several significant results that contribute to our knowledge of traditional herbal medicines in hypertension management. The molecular docking study showed strong binding interactions between selected phytochemicals and human renin, with binding energies comparable to known synthetic inhibitors. Particularly important were the interactions of Withaferin A and Withanone, which exhibited binding energies of -9.7 kcal/mol, suggesting their potential role as natural renin inhibitors. The identification of main interaction residues and binding modes provides valuable information for future drug design efforts targeting renin inhibition. The structure-activity relationships established in this study offer guidance for the development of more effective derivatives or analogues. The predicted pharmacokinetic parameters suggest good oral bioavailability and distribution characteristics, particularly for the withanolides.

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