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Molecular Docking Analysis of Natural Bioactive Compound Targeting Hypertension – Associated Proteins

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Abstract: *Hypertension is one of the most common chronic cardiovascular disorders worldwide and a major cause of morbidity and mortality. Persistent elevation of blood pressure contributes significantly to cardiovascular, renal, and cerebrovascular complications. Pulmonary arterial hypertension (PAH), a severe form of hypertension, is characterized by narrowing of pulmonary arteries, vascular remodeling, and increased pulmonary vascular resistance, which ultimately places excessive strain on the right side of the heart. The endothelin system, particularly endothelin receptor A (ETA) and endothelin receptor B (ETB), plays an important role in the pathogenesis and progression of hypertension through mechanisms involving vasoconstriction, endothelial dysfunction, and abnormal vascular proliferation. In addition, the renin–angiotensin system (RAS), especially angiotensin II and its AT1 receptor, is a key regulator of blood pressure and fluid balance, making it an important therapeutic target in hypertension management.*

Overall, this study highlights the significance of molecular docking as an efficient and cost-effective approach for identifying potential natural antihypertensive agents. The findings suggest that selected phytochemicals may serve as promising lead compounds for further experimental and clinical evaluation in the development of safer and more effective therapies for hypertension management.

Keywords: *Hypertension*

I. INTRODUCTION

Background

Hypertension is a major contributor to global morbidity and mortality. Research suggests that has the potential to lower blood pressure and protect against damage to vital organs. However, the specific biological targets it interacts with and the mechanisms through which it exerts these effects are still not fully understood.(1)

Pulmonary Arterial Hypertension (PAH) is a serious condition affecting the pulmonary arteries, characterized by narrowing of blood vessels, structural changes in the vascular wall, and formation of clots within the vessels. As the disease progresses, resistance to blood flow in the lungs increases, placing significant strain on the right side of the heart. This added workload can result in symptoms such as shortness of breath, chest discomfort, and persistent fatigue.(2)

molecular docking has gained importance as a foundational computational approach in the early stages of drug discovery for hypertension. It provides a theoretical framework to study the interaction between small molecules and specific protein targets involved in blood pressure regulation, such as angiotensin-converting enzyme (ACE), renin, and angiotensin II receptors. By predicting the binding orientation and affinity of potential drug candidates, docking helps researchers understand how these compounds may inhibit or modulate the activity of target proteins. Widely used tools like AutoDock and Discovery Studio facilitate the visualization and analysis of these molecular interactions.(3)

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The background application of molecular docking in hypertension research is particularly significant in the exploration of natural products and phytochemicals, which are considered promising sources of novel antihypertensive agents. This computational technique allows rapid screening of large compound libraries, reducing time, cost, and dependency on extensive laboratory experiments during the initial phases of drug development. As a result, molecular docking serves as a crucial step in identifying lead compounds with high binding potential, which can then be further evaluated through experimental studies to develop improved therapies for hypertension management.[4]

Introduction

Hypertension is a widespread and potentially life-threatening condition affecting roughly 30% of the global population. A key factor in its development is angiotensin (Ang), a hormone that plays a central role in regulating blood pressure. Two major classes of drugs commonly used to manage hypertension are Angiotensin-Converting Enzyme (ACE) inhibitors and Angiotensin Receptor Blockers (ARBs). ARBs work by blocking the interaction between angiotensin II (Ang II) and the angiotensin type-1 (AT1) receptor.[5]

Angiotensin II, the primary effector peptide of the renin-angiotensin system (RAS), is a major contributor to hypertension. Its effects are mediated through different receptor types.[6]

The AT1 receptor belongs to the G protein-coupled receptor (GPCR) family and is encoded by a gene located on human chromosome 3. In rats, two isoforms of this receptor—AT1A and AT1B—have been identified, sharing about 94% similarity. These receptors play a crucial role in maintaining blood pressure as well as fluid and electrolyte balance.[7]

The AT2 receptor is another member of the GPCR family that binds Ang II with similar affinity as AT1 receptors, although it shares only about 34% sequence similarity with AT1. It is highly expressed during fetal development but decreases significantly after birth. In adults, AT2 receptors are mainly found in the brain, heart, adrenal medulla, kidneys, and reproductive tissues.[8]

Hypertension affects roughly one-third of the global population and is a major contributor to cardiovascular and kidney diseases, making it a leading cause of early mortality. The World Health Organization recommends several first-line medications for managing high blood pressure, including thiazide and thiazide-like diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, and long-acting dihydropyridine calcium channel blockers. Among these, synthetic ACE inhibitors are commonly prescribed due to their strong and reliable antihypertensive effects. However, their use is often associated with side effects such as increased lipid levels, fluid and sodium retention, swelling of the ankles, persistent cough, flushing, and dizziness .As a result, there is growing scientific interest in identifying ACE-inhibiting compounds derived from natural food sources as potentially safer alternatives.[9]

Molecular docking has become an important computational strategy in hypertension research for identifying and optimizing potential drug candidates. This method predicts how small molecules, including natural compounds and synthetic drugs, bind to target proteins that play key roles in blood pressure regulation. Common targets in docking studies include angiotensin-converting enzyme (ACE), angiotensin II receptors, renin, and calcium channels. By simulating ligand–protein interactions, docking provides insights into binding affinity, orientation, and stability of the complex, which are critical factors in determining the effectiveness of a compound as an inhibitor or modulator. Software tools such as AutoDock and Schrödinger are frequently used to carry out these simulations and generate binding energy scores.[10]

In hypertension studies, molecular docking is especially valuable for screening phytochemicals from medicinal plants, as many natural compounds exhibit potential vasodilatory, antioxidant, or enzyme-inhibiting properties. The interactions identified through docking, including hydrogen bonding, hydrophobic contacts, and electrostatic forces, help researchers understand the mechanism of action at the molecular level. Furthermore, docking is often integrated with ADMET analysis to assess pharmacokinetic behavior and safety profiles of promising compounds. Overall, molecular docking offers a cost-effective and efficient approach for early-stage drug discovery, guiding the development of novel antihypertensive agents before experimental validation in laboratory and clinical settings.[11]

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Literature survey

Hypertension is one of the most common non-communicable diseases worldwide and is recognized as a major risk factor for cardiovascular, cerebrovascular, and renal disorders. According to global health reports, nearly one-third of the adult population is affected by elevated blood pressure, making hypertension a leading contributor to morbidity and premature mortality. Persistent hypertension damages blood vessels and vital organs, including the heart, kidneys, brain, and eyes, thereby increasing the risk of stroke, myocardial infarction, heart failure, and chronic kidney disease. Because of its asymptomatic nature during the early stages, hypertension is often referred to as a "silent killer."

Pulmonary Arterial Hypertension (PAH) is another severe form of hypertension characterized by progressive narrowing and remodeling of pulmonary arteries. The disease leads to increased pulmonary vascular resistance and excessive strain on the right ventricle of the heart, eventually causing right heart failure. Several studies have demonstrated that endothelin receptors play an important role in the pathogenesis of PAH.

Molecular docking is particularly useful in screening phytochemicals from medicinal plants because natural compounds often possess antihypertensive, antioxidant, anti-inflammatory, and vasodilatory activities. Docking analysis identifies important interactions such as hydrogen bonding, hydrophobic interactions, van der Waals forces, and electrostatic interactions between ligands and target proteins. Compounds with strong binding affinity and stable interactions are considered potential lead molecules for further experimental evaluation.

Several phytoconstituents have demonstrated promising antihypertensive potential through computational studies. Bioactive compounds such as ajmaline, serpentine, sarpagine, yohimbine, quercetin, luteolin, kaempferol, emodin, gallic acid, ellagic acid, and caffeic acid have shown favorable interactions with hypertension-related target proteins. These compounds are known for their antioxidant and vasoprotective properties, which may contribute to blood pressure regulation and cardiovascular protection. Phytochemicals containing flavonoids, alkaloids, tannins, phenolic acids, and glycosides have attracted particular attention because of their ability to modulate oxidative stress, endothelial dysfunction, and vascular inflammation.

The molecular docking workflow generally involves several systematic steps. Initially, the target protein is selected from the Protein Data Bank (PDB) based on parameters such as X-ray crystallographic resolution and organism source. Protein preparation includes removal of water molecules, addition of hydrogen atoms, and identification of the active binding site. Ligand structures are obtained from chemical databases such as PubChem and DrugBank and converted into suitable formats for docking. AutoDock tools are then used to prepare protein and ligand structures in PDBQT format, followed by docking execution using AutoDock Vina. Finally, docking interactions are analyzed and visualized using Discovery Studio to generate two-dimensional and three-dimensional interaction diagrams.

Current literature strongly supports the use of computational approaches in hypertension research because they provide valuable insights into molecular mechanisms and facilitate rapid identification of novel therapeutic agents. Molecular docking combined with ADMET analysis represents an efficient strategy for discovering natural antihypertensive compounds with improved efficacy and reduced toxicity.

Objective

1. Epidemiological Objective

To assess the prevalence, incidence, and demographic distribution of hypertension in a defined population, and to identify associated risk factors such as age, lifestyle, and genetic predisposition.

2. Pathophysiological Objective

To study the molecular and physiological mechanisms involved in hypertension, including vascular resistance, endothelial dysfunction, and hormonal regulation systems such as the renin-angiotensin system.

3. Pharmacological Objective

To evaluate the efficacy and safety of antihypertensive drugs (e.g., ACE inhibitors, beta-blockers, calcium channel blockers) in controlling blood pressure and reducing complications.

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4. Clinical Objective
To analyze diagnostic methods and treatment outcomes in hypertensive patients, and to determine the effectiveness of lifestyle modifications (diet, exercise, salt reduction).
5. Computational / Docking Objective To perform molecular docking studies of selected bioactive compounds against target proteins involved in hypertension, in order to identify potential inhibitors with high binding affinity and therapeutic potential.
6. Preventive Objective
To explore preventive strategies and public health interventions that can reduce the burden of hypertension and associated cardiovascular diseases.
Primary Objective:
1.To evaluate the therapeutic potential of selected compounds in the management of Hypertension through experimental and/or computational approaches.
Secondary Objectives:
2.To analyze the interaction between selected ligands and hypertension-related target proteins using molecular docking.[12]

Disease Importance

The importance of hypertension in research is closely linked to its widespread occurrence and its role as a major risk factor for cardiovascular diseases. Long-term hypertension significantly increases the risk of myocardial infarction, stroke, heart failure, atherosclerosis, chronic kidney disease, and peripheral vascular disorders. In many cases, hypertension remains asymptomatic during the early stages and is therefore often called a "silent killer." Delayed diagnosis and inadequate treatment contribute to serious complications and increased healthcare burden.[17]
Hypertension is a multifactorial disease influenced by genetic, environmental, physiological, and lifestyle-related factors. Sedentary lifestyle, obesity, excessive salt intake, smoking, alcohol consumption, stress, and aging are among the major contributors to elevated blood pressure. In addition, dysregulation of important physiological systems such as the renin–angiotensin–aldosterone system (RAAS), sympathetic nervous system, endothelial function, and calcium signaling pathways plays a central role in the development of hypertension. Understanding these mechanisms is essential for the development of effective therapeutic strategies.
Research on hypertension is highly important because currently available antihypertensive drugs may produce adverse effects such as dizziness, fatigue, electrolyte imbalance, cough, hypotension, and renal complications. Although several classes of drugs including Captopril, Losartan, Amlodipine, and Atenolol are widely used, some patients develop drug resistance or require combination therapy for effective blood pressure control.[13]
Modern computational techniques such as molecular docking, virtual screening, molecular dynamics simulation, and bioinformatics are widely applied in hypertension research. These methods help predict ligand–protein interactions and binding affinity against important targets such as ACE, angiotensin II type-1 receptor, renin, β-adrenergic receptors, and calcium channels. Computational approaches reduce research cost and time while helping researchers prioritize promising compounds for experimental validation.[14]
In conclusion, hypertension is an important area of biomedical and pharmaceutical research because of its increasing global prevalence, serious complications, and limitations associated with existing therapies. Continuous scientific research involving molecular studies, pharmacological investigations, and computational drug discovery is essential for developing safer and more effective antihypertensive treatments and reducing the worldwide burden of cardiovascular disease.[15]

Known Plant Activity

The flowers of Triphala constituent plants and Sarpagandha are gaining scientific attention for their potential role in the management of hypertension due to their rich phytochemical composition and therapeutic properties. Triphala is a well-

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known Ayurvedic formulation prepared from three medicinal plants, namely Terminalia chebula, Terminalia bellirica, and Emblica officinalis. While the fruits are traditionally used in medicine, the flowers of these plants also contain valuable bioactive compounds such as flavonoids, tannins, phenolic acids, and antioxidants. These phytochemicals are known to reduce oxidative stress, protect blood vessels from free radical damage, and improve endothelial function, all of which are important in maintaining normal blood pressure levels and promoting healthy cardiovascular function.

Similarly, the flowers of Sarpagandha (Rauvolfia serpentina) possess significant medicinal value because they contain alkaloids and secondary metabolites associated with antihypertensive activity. The plant is especially recognized for the presence of reserpine, a bioactive alkaloid that lowers blood pressure by decreasing sympathetic nervous system stimulation. Flower extracts of Sarpagandha may also exhibit calming, sedative, and vasodilatory effects, which help relax blood vessels, improve blood circulation, and reduce stress-related hypertension. In traditional herbal medicine, various parts of the plant, including the flowers, have been used to support nervous system relaxation and cardiovascular health.[16]

Gap : Combination not studied

The combination study of Triphala and Sarpagandha in diabetes research represents an important scientific gap in the field of herbal therapeutics and polyherbal drug development. Triphala is a classical Ayurvedic formulation composed of three medicinal fruits—Terminalia chebula, Terminalia bellirica, and Emblica officinalis. It has been widely reported for its antidiabetic, antioxidant, anti-inflammatory, and lipid-lowering properties. Several studies demonstrated that Triphala can reduce fasting blood glucose levels, improve lipid metabolism, and decrease oxidative stress in diabetic conditions. The formulation is also known to enhance insulin sensitivity and protect pancreatic β-cells due to the presence of tannins, flavonoids, gallic acid, ellagic acid, and vitamin C–rich phytoconstituents.

Sarpagandha (Rauwolfia serpentina) is traditionally recognized for antihypertensive, sedative, neuroprotective, and antioxidant activities. The plant contains important alkaloids such as reserpine, ajmaline, serpentine, and rescinnamine, which show significant pharmacological actions. Although Sarpagandha is mainly studied in hypertension and neurological disorders, some experimental evidence suggests that its antioxidant and metabolic regulatory effects may contribute to glucose regulation and reduction of diabetic complications. However, detailed studies exploring its direct mechanisms remain limited.

Despite the individual therapeutic importance of Triphala and Sarpagandha, there is a major lack of scientific research on their combined. This absence of combination-based research creates a significant gap in diabetes pharmacology and herbal medicine development.

Future research should therefore focus on phytochemical characterization, molecular docking studies, α-amylase and α-glucosidase inhibition assays, animal model experimentation, toxicity evaluation, and clinical trials of the Triphala–Sarpagandha combination. Investigations on insulin signaling pathways, inflammatory biomarkers, oxidative stress markers, and gene expression studies may further help in understanding the exact mechanism of action of this polyherbal combination in diabetes management. [17]

Molecular Docking Procedure

1.Protein Preparation

The initial stage of site-specific molecular docking involves preparing the protein structure for analysis. This begins by accessing the Protein Data Bank (PDB) to retrieve the required protein. A protein is then carefully selected according to the study's target, ensuring it meets quality standards, such as being resolved through X-ray diffraction with a resolution better than 2 Å. The source of the protein is also considered, with Homo sapiens commonly chosen for studies related to human biology. Once an appropriate structure is identified, it is downloaded from the protein data bank and saved in PDB file format using the available options. This prepared file can then be used for subsequent docking studies.

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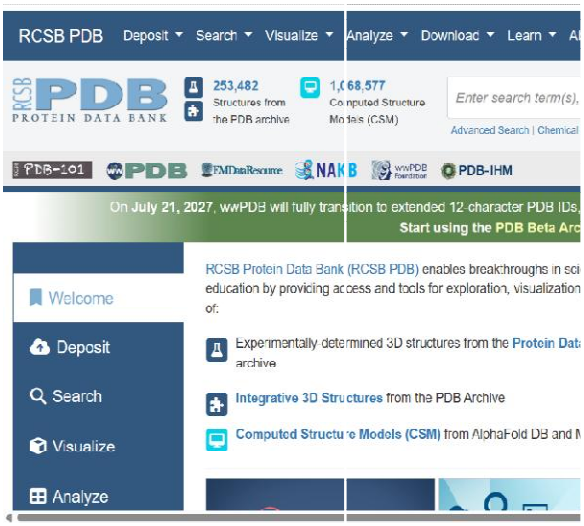

Access Protein Data Bank (PDB)
↓
Select target protein based on research objective
↓
Apply selection criteria:
↓
Download selected protein structure
↓
Right-click and choose PDB file format
↓
Save the file to local system

2. Ligand Preparation

The second step in molecular docking involves ligand preparation, where the compound of interest (drug) is selected and its structural data is obtained. Initially, the name of the drug is identified, and relevant information is searched in chemical databases such as DrugBank or PubChem. From DrugBank, the ligand structure can be downloaded and typically saved in PDB format. Alternatively, PubChem provides the option to download the compound in 3D SDF format, which contains detailed three-dimensional structural information. These downloaded ligand files are then used for further processing and analysis in the docking study.

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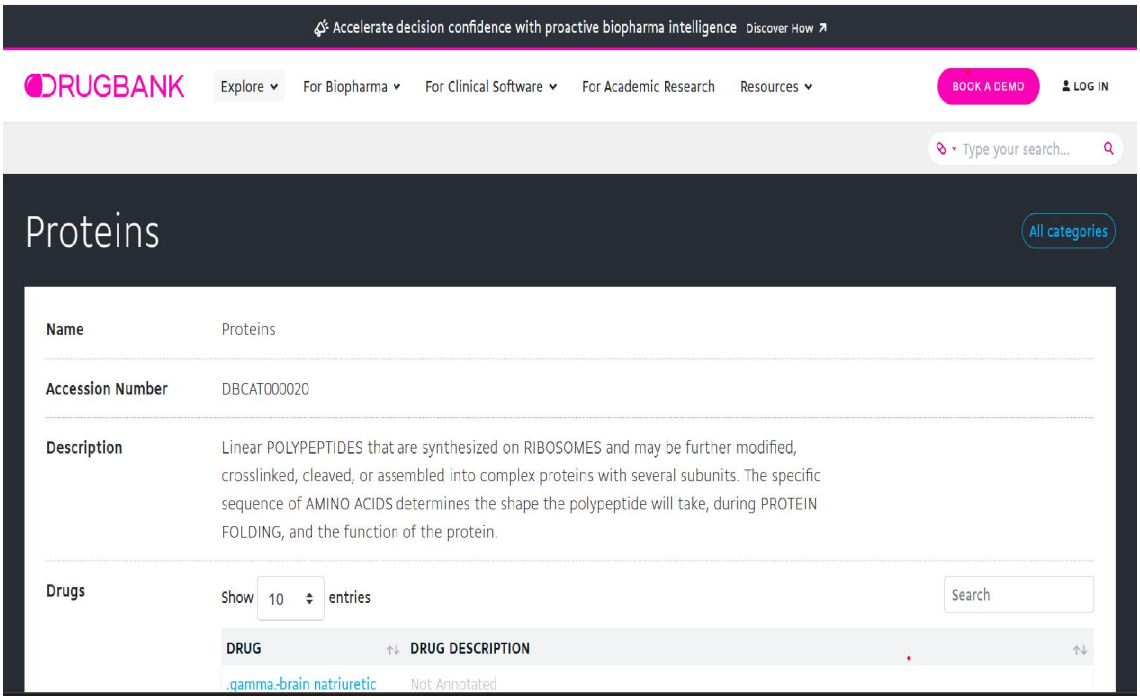

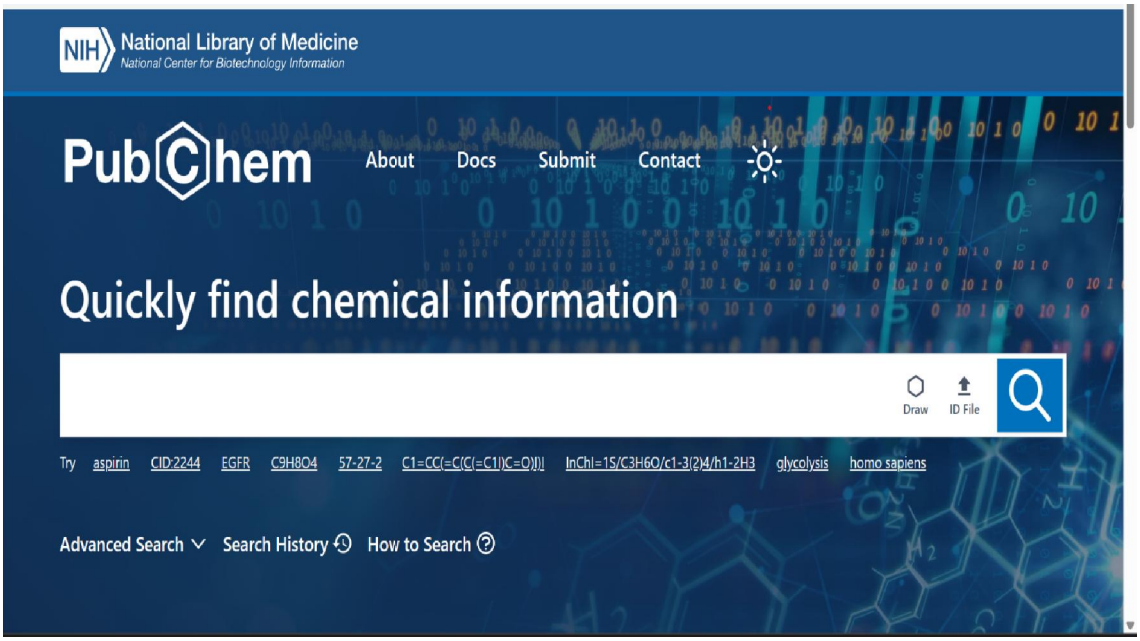

3. Drug Discovery Studio

The third step in the molecular docking workflow involves using Drug Discovery Studio for visualization and further processing of the protein structure. In this step, the software is opened and the required file is selected through the "File" option. The protein structure is then loaded into the workspace for analysis. Once the protein is displayed, the

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view can be adjusted by expanding the screen to obtain a clearer and more detailed visualization. This step helps in properly examining the protein structure before proceeding with docking and interaction studies.

In the subsequent step of molecular docking, the protein structure is refined and the binding site is defined using appropriate tools. Initially, all water molecules present in the structure are removed to avoid interference during docking. The ligand group within the protein is then expanded and selected for further analysis. Using the tools menu, receptor–ligand interactions are examined, and the binding site is defined and modified based on the selected region. A binding sphere is created from the current selection to represent the active site, and its size is adjusted by expanding or compressing it as required. After finalizing the sphere, its properties are accessed by right-clicking, allowing the user to note important parameters such as the radius and the X, Y, and Z coordinates. These details are essential for accurately setting up the docking process.

In this stage of molecular docking, the protein structure is further refined to prepare it for accurate analysis. Initially, any bound ligand present in the protein is removed to avoid interference with the docking process. The cleaned protein structure is then selected, and under the chemistry options, hydrogen atoms are added—particularly polar hydrogens—to improve the accuracy of interaction studies. After completing these modifications, the prepared protein is saved in Protein Data Bank (PDB) format for further use.

For ligand preparation, if the drug file is available in SDF format, it is opened using Drug Discovery Studio and then converted by saving it in PDB format. This ensures compatibility of both protein and ligand files for subsequent docking procedures.[17]

4. Docking Folder

In this step of the molecular docking procedure, a dedicated working directory is created to organize all necessary files. A new folder is made, typically in the Windows "C" drive, where all AutoDock Vina-related files and the configuration file are stored together for easy access. The configuration file is then prepared by specifying key parameters, including the receptor and ligand file names in PDBQT format, as well as the desired output file name. Additionally, the coordinates for the docking search space—center X, center Y, and center Z—are entered based on the previously determined binding site values. These parameters define the region where docking will occur. Finally, the output file is assigned an appropriate name, ensuring that all inputs are properly organized for running the docking simulation.

5. Autodock Folder

In this step, the prepared protein is processed using the AutoDock tool to make it suitable for docking. The procedure begins by opening the file and loading the molecule into the software using the "read molecule" option. Once loaded, the protein structure is displayed on the screen, allowing for visualization and selection. The macromolecule option is then chosen to define the protein for docking purposes, and grid settings are applied to specify the region of interest. The desired protein is selected by clicking on its name, and the molecule is confirmed for further processing. Finally, the prepared protein is saved in PDBQT format, which is required for compatibility with AutoDock-based docking simulations.

6. For Ligand Preparation

in this stage, the ligand is prepared for docking using the appropriate software tools. The process begins by selecting the ligand input file and opening it within the program. Once opened, the desired drug molecule is chosen, and its structure is displayed on the screen for visualization. After confirming the correct ligand, it is processed and directed to the output option, where it is saved in PDBQT format, which is required for docking studies. It is important to note that both the prepared protein and ligand files, now in PDBQT format, should be stored together in the designated docking folder, ensuring proper organization and readiness for the docking simulation.

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7. Command Prompt

In this step, the molecular docking process is executed using the command prompt. First, the command prompt is opened, and the path of the docking folder is copied and navigated to by typing the "cd" command followed by the folder address. Once inside the correct directory, the functionality of AutoDock Vina can be checked by running the command "vina.exe --help," where the double hyphen indicates command options. After confirming proper setup, the docking process is initiated by executing the command "vina.exe --config conf.txt --log log.txt," which uses the configuration file and generates a log file of the docking results. This completes the docking execution and prepares the results for further analysis.

8. 2D,3D Structure of Protein

In this final step, Drug Discovery Studio is used to analyze the docking results and visualize molecular interactions. The prepared protein structure in PDBQT format, along with all the split ligand poses generated after docking, is loaded into the software. The interaction analysis option is then selected to study how the ligand binds with the protein. A specific ligand pose is chosen, defined, and examined for its interactions within the active site. The interaction details, particularly non-bonded interactions, are visualized by selecting the appropriate display options. To explore different docking poses, the user can navigate through them using the up and down arrows. Additionally, a two-dimensional (2D) interaction diagram can be generated for clearer representation, which can then be saved as an image file for documentation and further analysis. In this step, a high-quality three-dimensional (3D) visualization of the protein–ligand complex is generated for presentation or publication purposes. The process begins by accessing the visualization or script options within the software and selecting settings that enhance the image to publication-quality standards.[18]

ADMET Properties Of Phytoconstituent

PHYTOCONSTITUENT	LIPINSKI	BIOAVAILABILITY	TOXICITY PREDICTIONS	GEL ABSORPTION	BBB PERMANT
AJMALINE	YES	O.55	NO	HIGH	YES
CAFFEIC ACID	YES	O.56	NO	HIGH	NO
CHRYSOPHENOL	YES	0.55	NO	HIGH	NO
ELLAGIC ACID	YES	O.55	NO	HIGH	NO
EMODIN	YES	O.55	NO	HIGH	NO
GALLIC ACID	YES	0.56	NO	HIGH	NO
KAEMPFEROL	YES	0.55	NO	HIGH	NO
LUTEOLIN	YES	0.55	NO	HIGH	NO
QUERCETINE	YES	0.55	NO	HIGH	NO
RESCINNAMINE	NO	0.17	NO	HIGH	NO
RESERPINE	NO	0.17	NO	HIGH	NO
RHEIN	YES	0.56	NO	HIGH	NO
RUTIN	NO	0.17	NO	LOW	NO
SARPAGINE	YES	0.55	NO	HIGH	YES
SERPENTINE	YES	0.56	NO	HIGH	YES
YOHOMBINE	YES	O.55	NO	HIGH	YES

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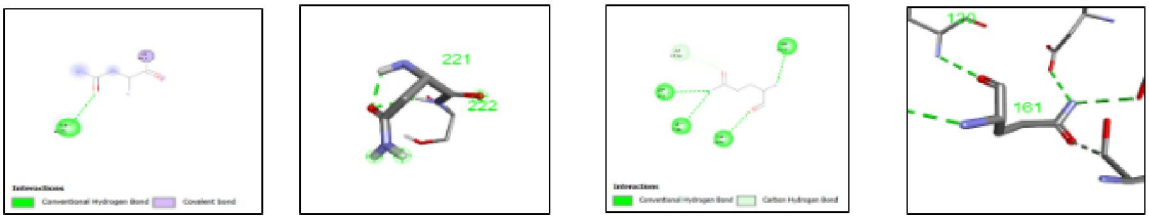
Intraction Diagram

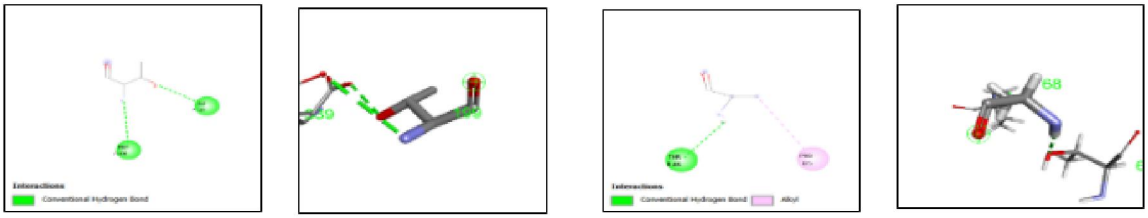
1FMK

2D **3D** **2D** **3D**



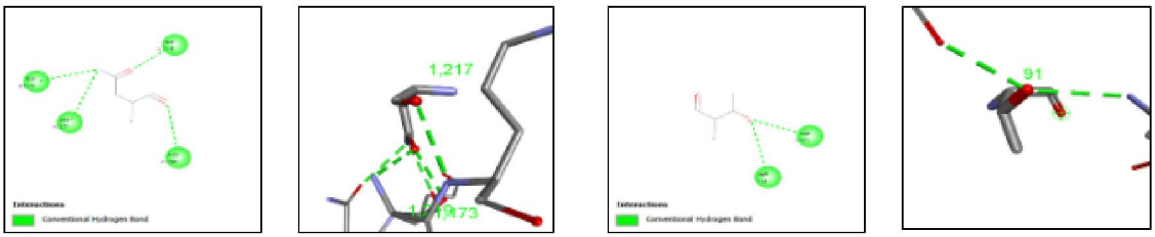
4X30 **5CRI**

2D **3D** **2D** **3D**



6CEN **6SFI**

2D **3D** **2D** **3D**



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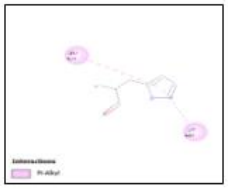
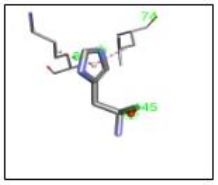
7B9L

2D



3D



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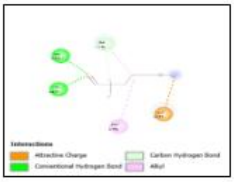

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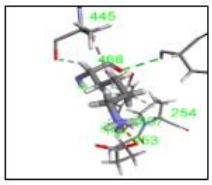

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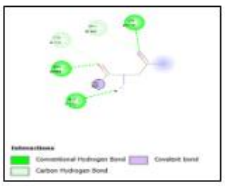
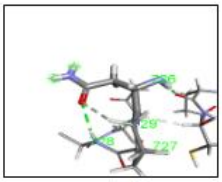
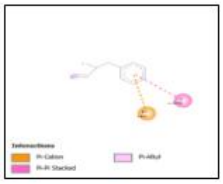


3D

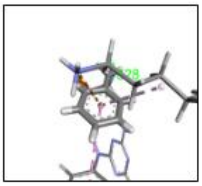


8BAB

2D



3D



Result

Binding Energy Table

PHYTOCONSTITUENT	1FMK	2CJY	4X30	5CRI	6CEN	6SFI	7B9L	7SJT	8B8U	8BAB
AJMALINE	-5.6	-5.1	-5.1	-5.8	-3.9	-6.9	-5.7	-5.4	-6.9	-6.4
CAFFEIC ACID	-4.8	-4.4	-4.5	-4.5	-3.4	-5.9	-5.0	-5.0	-5.8	-5.6
CHRYSOPHENOL	-5.4	-5.8	-5.5	-5.9	-3.4	-6.9	-5.0	-5.4	-6.7	-6.1
ELLAGIC ACID	-5.1	-5.0	-4.9	-6.4	-3.7	-6.6	-4.9	-5.6	-7.0	-6.6
EMODIN	-5.3	-4.8	-5.0	-6.5	-3.9	-6.7	-5.2	-5.1	-7.3	-6.3
GALLIC ACID	-5.7	-5.3	-5.3	-5.8	-3.9	-7.3	-5.5	-5.8	-7.2	-6.7
KEAMPFEROL	-5.8	-5.4	-5.0	-5.8	-3.8	-7.1	-5.2	-6.0	-7.1	-6.6
LUTEOLIN	-5.8	-4.8	-4.9	-5.6	-3.8	-6.4	-5.4	-5.2	-7.3	-6.7
QUERCETINE	-5.0	-4.4	-5.0	-5.6	-3.5	-6.6	-5.1	-5.5	-7.0	-6.7
RESCINNAMINE	-5.1	-4.1	-4.6	-5.7	-4.3	-7.1	-5.4	-6.1	-6.1	-6.3
RESERPINE	-5.4	-5.0	-5.6	-6.0	-4.0	-7.4	-5.7	-5.8	-6.6	-6.5
RHEIN	-5.4	-4.7	-5.0	-6.0	-3.7	-6.8	-5.7	-5.2	-7.8	-6.7
RUTIN	-5.3	-5.2	-7.3	-6.9	-4.7	-7.6	-6.0	-7.0	-8.3	-7.9
SARPAGINE	-6.1	-5.2	-5.9	-6.1	-4.1	-7.7	-5.8	-5.8	-6.9	-7.5
SERPENTINE	-5.2	-4.6	-5.4	-6.0	-3.7	-6.9	-5.5	-0.3	-6.5	-7.4
YOHIMBINE	-5.2	-4.9	-5.4	-5.8	-3.9	-7.3	-5.8	-5.6	-6.9	-6.5
AMLODIPINE (S.D)	-4.7	-4.0	-4.8	-4.8	-3.2	-6.1	-5.0	-4.9	-6.0	-6.1

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The molecular docking study was carried out to evaluate the binding affinity of various phytoconstituents against different target proteins, namely 1FMK, 2CJY, 4X30, 5CRI, 6CEN, 6SFI, 7B9L, 7SJT, 8B8U, and 8BAB. The docking scores obtained indicate the strength of interaction between the ligands and target proteins, where more negative binding energy values represent stronger and more stable interactions.

Among all the phytoconstituents studied, rutin exhibited the strongest binding affinity against most of the target proteins, with docking scores of −7.3 against 4X30, −6.9 against 5CRI, −7.6 against 6SFI, −7.0 against 7SJT, −8.3 against 8B8U, and −7.9 against 8BAB. These values were significantly better than the standard drug Amlodipine, which showed comparatively lower docking scores ranging from −3.2 to −6.1. The excellent binding affinity of rutin may be attributed to the presence of multiple hydroxyl groups capable of forming strong hydrogen bond interactions with amino acid residues present at the active site of the proteins.

Sarpagine also demonstrated promising activity, particularly against 1FMK, 6SFI, and 8BAB, with docking scores of −6.1, −7.7, and −7.5 respectively, indicating better interaction than the standard drug. Similarly, gallic acid showed strong affinity toward 6SFI and 8B8U with docking scores of −7.3 and −7.2, while luteolin and rhein exhibited notable binding against 8B8U with values of −7.3 and −7.8 respectively. Rhein displayed one of the highest affinities toward 8B8U, suggesting stable ligand–protein complex formation. Kaempferol also showed considerable inhibitory potential with docking scores of −7.1 against both 6SFI and 8B8U.

Discussion

Hypertension remains one of the leading causes of cardiovascular morbidity and mortality worldwide and continues to be a major public health challenge. Persistent elevation of arterial blood pressure contributes significantly to the development of cardiovascular diseases, renal dysfunction, stroke, and pulmonary arterial hypertension (PAH). The present study focused on understanding the molecular basis of hypertension and evaluating the therapeutic potential of selected phytoconstituents through molecular docking and ADMET analysis.

Pulmonary arterial hypertension is characterized by progressive narrowing and remodeling of pulmonary blood vessels, resulting in increased pulmonary vascular resistance and excessive workload on the right ventricle of the heart.

The renin–angiotensin system (RAS) also plays a central role in blood pressure regulation. Angiotensin II, acting mainly through AT1 receptors, promotes vasoconstriction, sodium and water retention, sympathetic activation, and vascular remodeling. Due to these effects, ACE inhibitors and angiotensin receptor blockers (ARBs) are widely used in hypertension treatment. In the present study, molecular docking was employed as a computational strategy to predict the interactions between selected phytoconstituents and hypertension-related target proteins. Molecular docking provides valuable information regarding ligand binding orientation, binding affinity, and molecular stability within the active site of target proteins. The use of AutoDock Vina and Discovery Studio enabled efficient visualization and analysis of protein–ligand interactions, including hydrogen bonding, hydrophobic interactions, and electrostatic contacts. Such interactions are essential for determining the inhibitory potential and therapeutic effectiveness of bioactive compounds.

The selected phytoconstituents, including ajmaline, caffeic acid, chrysophanol, ellagic acid, emodin, gallic acid, kaempferol, luteolin, quercetin, sarpagine, serpentine, and yohimbine, demonstrated promising pharmacokinetic characteristics based on ADMET analysis. Most compounds satisfied Lipinski's rule of five, suggesting favorable drug-likeness properties. Additionally, many compounds exhibited acceptable bioavailability scores and high gastrointestinal absorption, indicating their potential for oral administration. Blood–brain barrier permeability was absent in most compounds, which may reduce the possibility of central nervous system side effects, although compounds such as ajmaline, sarpagine, serpentine, and yohimbine showed BBB permeability. Rutin, reserpine, and rescinnamine.

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II. CONCLUSION

Hypertension remains one of the most significant cardiovascular disorders worldwide and contributes greatly to global morbidity and mortality. The disease involves complex mechanisms associated with vascular dysfunction, activation of the renin–angiotensin system, and endothelin-mediated vasoconstriction. Current antihypertensive therapies, although effective, are often associated with adverse effects, creating the need for safer and more effective alternatives derived from natural sources.

The present study highlights the importance of molecular docking as an efficient computational approach for identifying potential antihypertensive agents. Through docking analysis, the interactions between selected phytoconstituents and hypertension-related target proteins were successfully evaluated. The study also demonstrated the usefulness of ADMET analysis in predicting pharmacokinetic behavior, gastrointestinal absorption, bioavailability, toxicity, and blood–brain barrier permeability of the selected compounds.

Among the investigated phytoconstituents, several compounds showed favorable Lipinski properties, good bioavailability, high gastrointestinal absorption, and promising binding potential toward target proteins involved in blood pressure regulation. These findings suggest that natural bioactive compounds may serve as effective lead molecules for the development of novel antihypertensive drugs with improved safety profiles.

In conclusion, molecular docking combined with ADMET prediction provides a rapid, reliable, and cost-effective strategy for early-stage antihypertensive drug discovery. The selected phytochemicals demonstrated promising therapeutic potential and may contribute to the future development of safer and more effective treatments for hypertension and related cardiovascular disorders. However, further experimental validation through in vitro, in vivo, and clinical studies is essential to confirm their efficacy and safety.

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