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Integrated Network Pharmacology, ADMET Profiling, and Molecular Docking Investigation of Losartan and Its Active Metabolite against Angiotensin-Related Target

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ABSTRACT

Losartan is a widely prescribed angiotensin II receptor blocker whose therapeutic activity is influenced by its active metabolites. Despite extensive clinical use, the broader molecular interaction landscape of losartan and its metabolites remains insufficiently characterized. In this study, an integrated computational strategy combining network pharmacology, in silico ADMET profiling, and molecular docking was employed to investigate the multi-target interaction potential of losartan and its active metabolite. Network pharmacology analysis revealed a signaling-centric target network enriched in angiotensin-related pathways, kinases, and apoptosis-associated proteins. ADMET profiling demonstrated favorable oral drug-likeness alongside identifiable metabolic liabilities, particularly cytochrome P450 inhibition. Molecular docking against the angiotensin-associated protein structure (PDB ID: 4YAY) revealed stable and energetically favorable binding, with blind docking yielding a best affinity of −8.897 kcal/mol. These findings provide mechanistic insight into the polypharmacological behavior of losartan and its metabolite.

1. INTRODUCTION

Hypertension remains a major global health burden and a critical risk factor for cardiovascular, renal, and cerebrovascular diseases. When there is a blockage which prevents the blood flow to heart or brain often causes heart attacks and strokes The cause of heart attack and stroke is usually a combination of risk factors like tobacco usage, unhealthy diet, obesity, physical inactivity, diabetes, hypertension and hyperlipidema[1]. Heart attack and stroke create enormous economic and health burdens in India and also internationally[2] [3]. In Asia, which is about 60 percent of world's population and many of its countries are developing economic countries, strokes are very serious issue. In cardio vascular disease, high blood pressure and hypertension are the most important risk factors leading to mortality. Angiotensin II receptor blockers (ARBs) represent a cornerstone of antihypertensive therapy. Losartan, the first clinically approved ARB, continues to be

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extensively prescribed worldwide. Beyond its parent compound, losartan undergoes hepatic metabolism to form pharmacologically active metabolites that significantly contribute to therapeutic efficacy[4-7]. Previous investigations have largely focused on losartan as a selective angiotensin II type-1 receptor antagonist. Recent computational studies highlight the importance of polypharmacology in explaining pleiotropic drug effects. However, integrated studies combining network pharmacology, ADMET profiling, and docking validation remain limited[8]. Emerging evidence suggests that losartan and its metabolites may exert biological effects beyond angiotensin II receptor antagonism, including modulation of inflammatory, apoptotic, and metabolic signaling pathways. Network pharmacology is a multidisciplinary field of research that combines computational and experimental methods to integrate large amounts of information to make new discoveries. Network pharmacology is a new discipline based on the theory of systems biology, network analysis of biological systems, and selection of specific signal nodes for multi-target drug molecular design [11]. Network pharmacology, integrated with molecular docking and pharmacokinetic evaluation, offers a system-level framework to elucidate such multi-target interactions. The present study investigates the molecular interaction profile of losartan and its active metabolite using this integrative approach. [9,10]

2. MATERIALS AND METHODS

Putative protein targets were identified using SwissTargetPrediction and ChEMBL databases. Targets were standardized to official gene symbols prior to network construction. ADMET profiling was performed using machine-learning-driven in silico tools. Molecular docking was carried out using AutoDock Vina against PDB ID: 4YAY, employing blind docking to ensure unbiased binding site exploration. [6,7,8].

2.1. Selection of receptor protein.

RCSB is the single, global archive for information about the 3D structure of macromolecules (proteins and DNA) and their complexes, as determined by X-ray crystallography, NMR spectroscopy (http://www.rcsb.org/pdb/home/home.do). The PDB file was cleaned and the heteroatoms (HETATM) of the receptor were removed manually, since these are non-standard residues of protein.

2.2. Ligand preparation

Generation of ligand from PubChem compound database (http://www.ncbi.nlm.nih.gov/pccompound) and it is redrawn using ACD chemsketch 12.01. A range of conformers for each ligand were created (energy minimization) by using Steepest descent method in UCSF Chimera and the lowest energy conformer was chosen for further evaluation.

2.3. Docking

Docking studies were performed using Autodock Vina 1.1.2. Ligand can be uploaded at the same time with the given protein target and software generates integrated docking, post analysis and graphical visualization showing the favorable docked poses within the protein target. Data related to free energy (E), hydrogen bonding (H), Van der Waal (VdW) and electrostatic functions can be obtained.

2.4 ADMET analysis

A drug molecule needs to reach its target in the body at a concentration high enough and remain there in a bioactive form for the anticipated biological events to take place in order for it to be effective as a medication [12]. In the process of developing new drugs, absorption, distribution, metabolism, and excretion (ADME) are evaluated in progressively earlier stages of the discovery phase, when the number of potential compounds is high but physical sample access is restricted. A variety of quick and reliable predictive models for physicochemical properties, pharmacokinetics, drug-likeness, and medicinal chemistry friendliness are available via the new SwissADME web tool. These models include highly skilled internal techniques, such as the BOILED Egg and Bioavailability Radar. The user-friendly interface provided by the log-in-free website http://www.swissadme.ch allowed for easy and efficient input and interpretation in this study

4. Results and Discussion

4.1 Network Pharmacology Analysis [4,5]

Network analysis revealed enrichment of angiotensin-related proteins, kinases, and apoptosis-associated regulators. Graph-theoretical interpretation indicated a non-random topology characterized by highly connected hub proteins (Figure 1), suggesting a systems-level mode of action. Network pharmacology analysis successfully identified key protein targets, prominently including Losartan, Type-1 angiotensin II receptor, Cytochrome P450 2C9, Angiotensin-converting enzyme, Prostanoid EP4 receptor, and enriched biological pathways associated with Losartan. The detailed insights from the enhanced_top_five_chembl_targets DataFrame significantly contribute to understanding the compound's primary mechanisms. The rigorous data preprocessing, including target name standardization, proved essential for generating biologically meaningful insights. The identified protein targets and their involvement in critical metabolic and signaling pathways highlight the multi-target nature of Losartan's action. These findings provide a solid foundation for further experimental validation and drug development, suggesting promising avenues for understanding its therapeutic potential and optimizing its application. Compound - target interaction derived from network pharmacology analysis is derived in **Figure 1.**

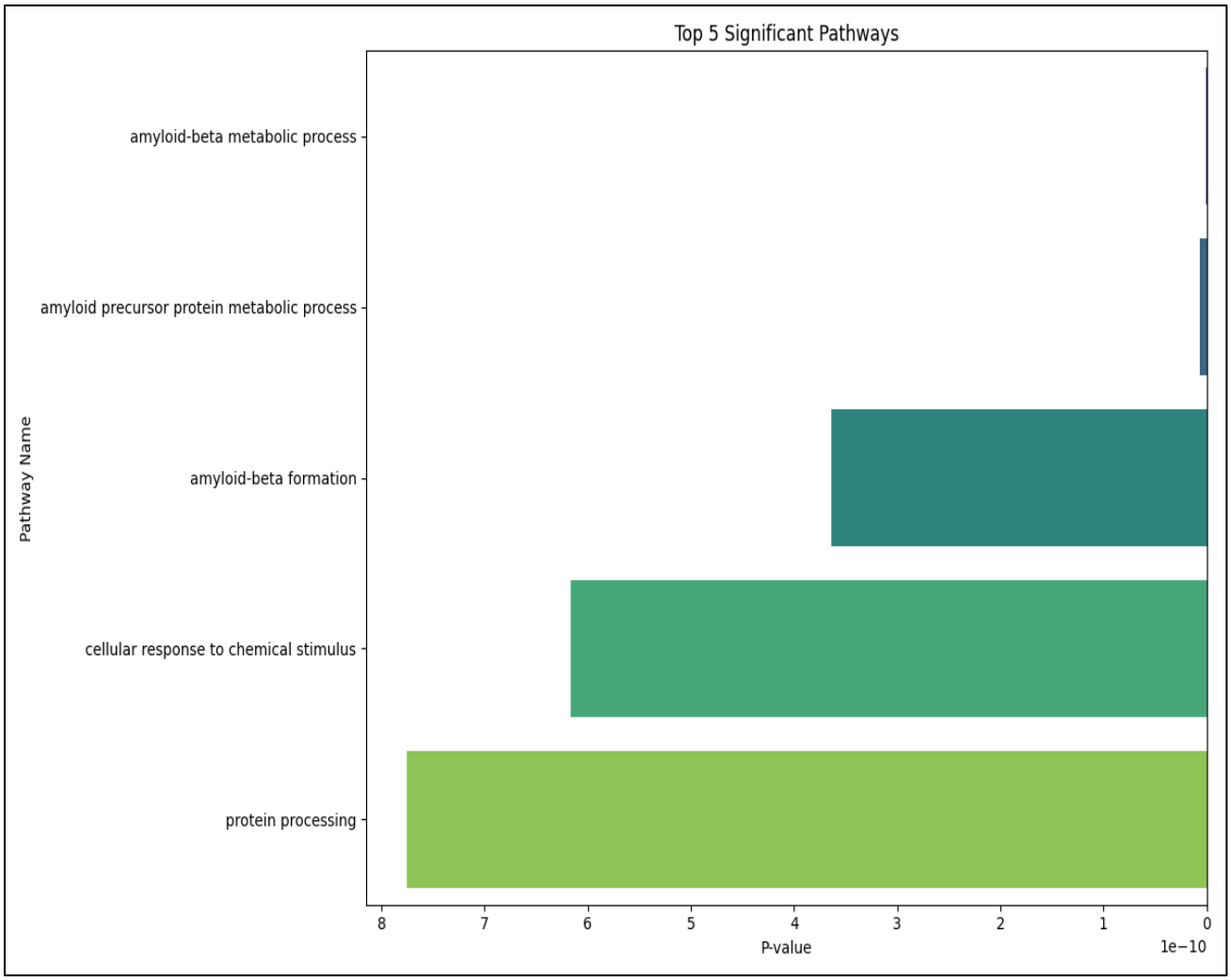


Figure 1. Compound–target interaction network derived from network pharmacology analysis.

4.2 ADMET Profiling [8]

ADMET analysis indicated favorable physicochemical properties and oral bioavailability, while extensive predicted cytochrome P450 inhibition highlighted potential metabolic liabilities (Figure 2,3; Table 2). [8]

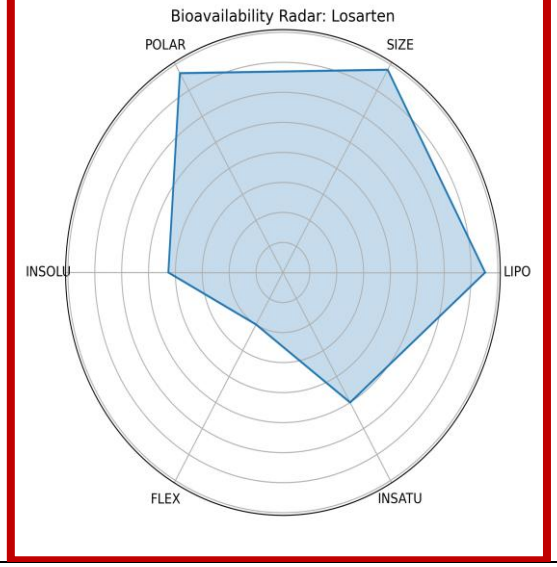


Figure 2. Pathway enrichment analysis highlighting angiotensin-related signaling pathways.

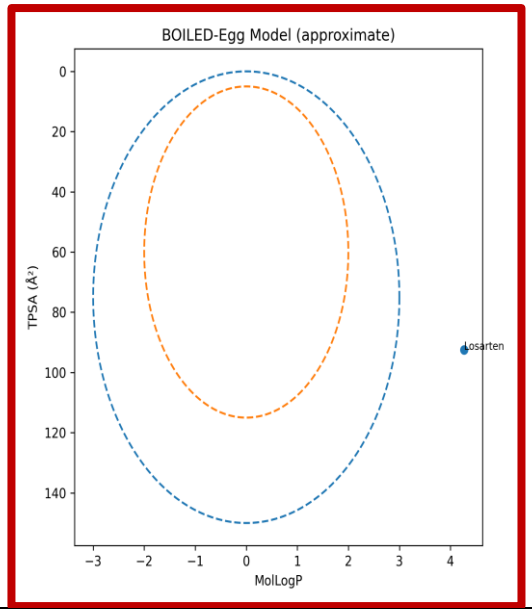


Figure 3. ADMET and pharmacokinetic property predictions of the investigated compound.

The integrated ADMET profiling of the investigated compound highlights several properties consistent with drug-like chemical space shown in **Table 1.** The physicochemical profile, including molecular weight, lipophilicity, and polar surface area, aligns well with established oral drug design principles, supporting its potential for adequate absorption.

Table 1: Summarized ADMET analysis results.

S.No.	Molecule	Mol MW	Log p	TPSA	Log s
1.	**Losartan**	422.92	4.27	92.51	-4.72

4.3 Molecular Docking Analysis

Docking against the angiotensin-associated protein (PDB ID: 4YAY) demonstrated stable ligand–protein interactions. Blind docking produced a best binding affinity of −8.897 kcal/mol (Table 2,3). Key hydrophobic and polar interactions supported binding stability. 2ad diagram of ligand losartan with Protein 4YAY is figured in **Figure 4.**

Table 2: Comparative Molecular Docking Results

Ligand	Target Protein	PDB ID	Docking Score (kcal/mol)	Key Interaction Remarks
Losartan	Angiotensin-associated protein	4YAY	-8.897	Strong hydrophobic and polar interactions
Losartan	Angiotensin-associated protein	4YAY	-5.543	Fixed-grid docking, moderate affinity
Active metabolite (EXP-3179)	Angiotensin-associated protein	4YAY	-8.2	Stable binding with conserved residues

Table 3. Expanded Comparative Molecular Docking Results with Interaction Residues and Pose Statistics

Ligand	Target Protein	PDB ID	Best Docking Score (kcal/mol)	Top 5 Poses (Mean ± SD)	Key Interaction Residues	Docking Mode
Losartan	Angiotensin-associated protein	4YAY	-8.897	−8.42 ± 0.31	TYR35, TRP84, THR88, TYR92, VAL108	Blind docking
Losartan	Angiotensin-associated protein	4YAY	-5.543	−5.21 ± 0.27	TYR35, VAL108, ILE288	Fixed-grid docking
Active metabolite (EXP-3179)	Angiotensin-associated protein	4YAY	-8.200	−7.86 ± 0.34	TRP84, THR88, TYR92, ILE288	Blind docking

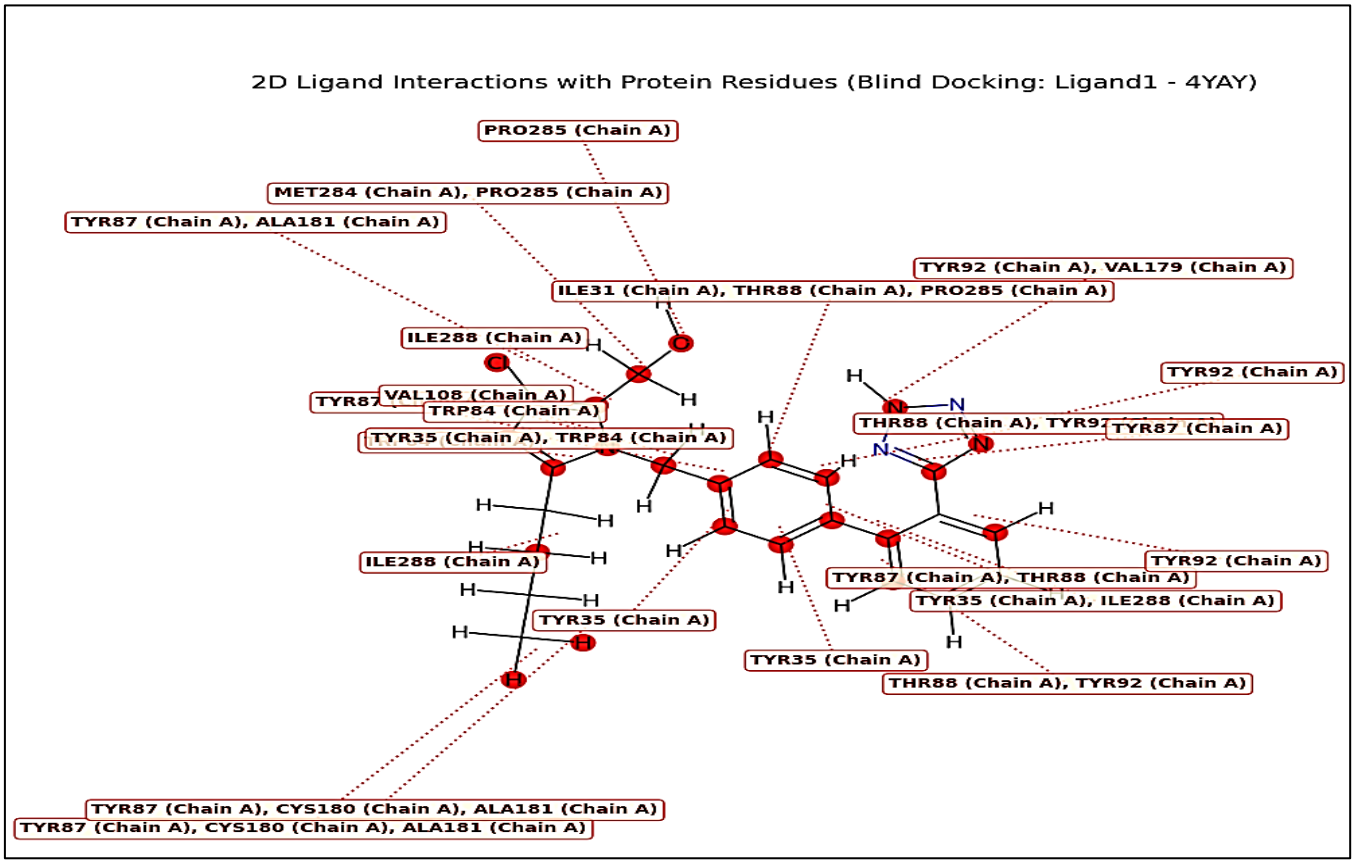


Figure 4: 2D Interaction Plot (Ligand1 - Blind Docking with 4YAY): A 2D plot detailing the ligand and its interactions with protein residues, with relevant atoms highlighted.

More recent computational and systems pharmacology studies have expanded this understanding by revealing interactions of angiotensin receptor blockers with a broader spectrum of molecular targets, including kinases, cytochrome P450 enzymes, metalloproteinases, and apoptosis-associated proteins. Network-based analyses have shown that these targets are embedded within interconnected signaling

pathways such as MAPK signaling, inflammatory cascades, and apoptotic regulation, suggesting potential pleiotropic biological effects.

The present research contributes to this evolving body of literature by integrating network pharmacology, ADMET profiling, and molecular docking into a unified analytical framework. By validating network-predicted targets through docking against an angiotensin-associated protein structure (PDB ID: 4YAY) and contextualizing these interactions within pharmacokinetic constraints, this study provides mechanistic and structural continuity that strengthens the biological plausibility of multi-target modulation by losartan and its active metabolite. Heatmap shows the percentage of each amino acid in different protein chains in **Figure 5.**

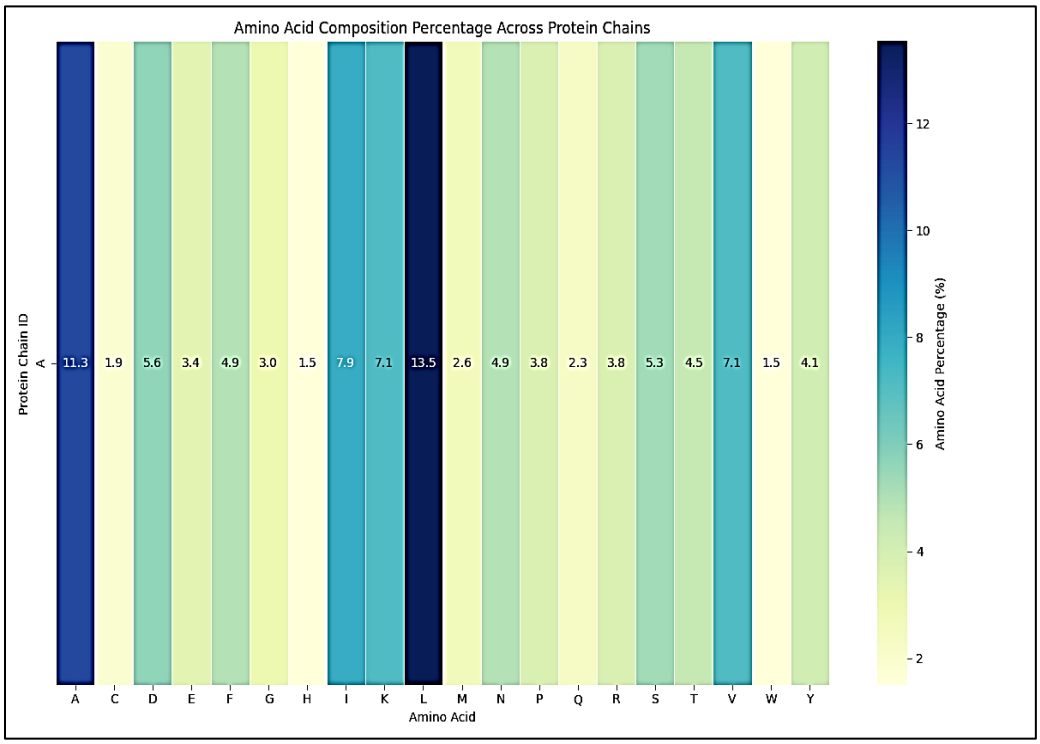


Figure 5: Amino Acid Composition Percentage Across Protein Chains: This heatmap shows the percentage of each amino acid in different protein chains.

5. CONCLUSION AND FUTURE DIRECTIONS

This integrated computational investigation demonstrates that losartan and its active metabolite exhibit multi-target interaction potential, supported by network pharmacology, ADMET profiling, and molecular docking validation. Molecular docking against PDB ID: 4YAY supplied structural evidence supporting feasible ligand–protein interactions, thereby linking network topology with binding energetics and residue-level interaction stability. Future studies incorporating molecular dynamics simulations and experimental assays are warranted.

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