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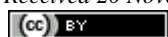
Uncovering multi-target natural inhibitors for hypertension through network pharmacology and structure-based screening

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Abstract

Hypertension is a major global health challenge and a key risk factor for cardiovascular, renal, and cerebrovascular disorders. Despite the availability of several synthetic antihypertensive drugs, their prolonged use often leads to adverse side effects, underscoring the need for safer alternatives. Natural compounds represent a promising source of bioactive molecules with potential therapeutic efficacy. Given the multifactorial nature of hypertension, multi-target therapeutic strategies may offer improved disease management. This study employed an integrative computational approach combining network pharmacology and structure-based analyses to identify potential protein targets and natural compounds relevant to hypertension. A total of 22 protein targets associated with hypertension-related pathways were identified. Virtual screening and pharmacokinetic (ADME) evaluations revealed 16 phytochemicals with strong binding affinities, among which 10 exhibited favorable drug-likeness and multi-target interaction profiles. Overall, the findings highlight several natural compounds as promising antihypertensive candidates with polypharmacological potential and a lower likelihood of adverse effects compared to conventional drugs. Experimental validation of the identified targets and lead compounds is warranted to confirm their therapeutic efficacy.

Keywords hypertension; network pharmacology; druggability; natural lead compounds; molecular docking; polypharmacology.

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1 Introduction

Hypertension (high blood pressure; HTN) is a major global health challenge and one of the leading risk factors for cardiovascular morbidity and mortality (Zhang and Qi, 2025). It is characterized by a sustained elevation of arterial pressure, where the force of circulating blood against arterial walls remains persistently high. According to the *Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7)*, normal blood pressure is defined as systolic blood pressure (SBP) <120 mmHg and diastolic blood pressure (DBP) <80 mmHg (Chobanian et al., 2003). Individuals with SBP

between 120–139 mmHg and/or DBP between 80–89 mmHg are considered prehypertensive (Kumar et al., 2016), whereas SBP >180 mmHg and DBP >120 mmHg represent a severe hypertensive crisis.

Prehypertension serves as an early indicator of the potential onset of hypertension (Erem et al., 2009). Often termed the “silent killer,” hypertension remains asymptomatic in its early stages but may eventually cause severe damage to vital organs such as the heart, kidneys, and brain. Globally, an estimated 1.28 billion adults aged 30–79 years are hypertensive, of whom nearly 46% are unaware of their condition (World Health Organization [WHO], 2023). In India, approximately 200–250 million individuals are affected (Gupta & Ram, 2022). According to data from the *National Family Health Survey-5 (NFHS-5, 2019–2020)*, hypertension prevalence is slightly higher in men ($\approx 24\%$) than in women ($\approx 21\%$) (National Family Health Survey [NFHS], 2022).

The development of hypertension is influenced by a combination of modifiable and non-modifiable risk factors. Modifiable factors include obesity, poor diet, physical inactivity, psychological stress, smoking, and excessive alcohol consumption, whereas non-modifiable factors comprise age, sex, race, and genetic predisposition (Princewell et al., 2019). Despite the availability of multiple classes of antihypertensive drugs, most are synthetic in origin and can cause adverse side effects or long-term complications. Consequently, the identification of safe, effective, and naturally derived compounds with antihypertensive potential represents an emerging focus in drug discovery.

In the present study, potential therapeutic targets associated with hypertension were identified through comprehensive bioinformatics analyses of key biological pathways, including the Renin–Angiotensin System (RAS), Aldosterone Synthesis and Secretion, and Aldosterone-Regulated Sodium Reabsorption pathways. The selection of candidate proteins was based on the concept that ideal drug targets are not always direct disease-causing entities but are often disease-modifying in nature (Katara, 2020).

The RAS plays a central role in blood pressure regulation and fluid homeostasis (Toke et al., 2001; Krishna et al., 2024). Increased RAS activity elevates angiotensin II (Ang II) levels, stimulating aldosterone secretion and contributing to vasoconstriction, elevated blood pressure, and progressive cardiovascular and renal damage (Paul et al., 2006). The Aldosterone Synthesis and Secretion pathway also plays a critical role in maintaining sodium and water balance through aldosterone, a mineralocorticoid hormone secreted by the zona glomerulosa of the adrenal cortex. Dysregulation of aldosterone—either hypo- or hypersecretion—can result in hypotension or hypertension, respectively (Bollag, 2014).

Similarly, the Aldosterone-Regulated Sodium Reabsorption pathway significantly contributes to hypertension pathophysiology. Elevated aldosterone levels enhance sodium reabsorption in renal epithelial cells via the epithelial sodium channel (ENaC), thereby increasing blood pressure (Tsilosani et al., 2022). This pathway is also associated with oxidative stress, inflammation, and fluid imbalance, linking it to various cardiovascular and renal disorders.

Bioinformatics provides powerful computational resources and methodologies—such as network-based and structure-based analyses—for the identification and evaluation of potential drug targets (Katara, 2013; Wishart, 2016; Zhang, 2018; Zhou et al., 2019). Comprehensive natural compound databases, particularly those focusing on plant-derived metabolites, offer access to a diverse repertoire of bioactive molecules with therapeutic potential (Kim et al., 2021). The utilization of such natural compounds as multi-target therapeutic agents may enhance treatment efficacy, accelerate recovery, and reduce toxicity and adverse drug reactions (Newman and Cragg, 2020).

Considering the global burden of hypertension and the limitations of existing antihypertensive therapies, the present study integrates bioinformatics-driven network pharmacology and structure-based screening approaches to (i) identify key protein targets implicated in hypertension-related pathways, and (ii) screen and

characterize natural lead compounds with potential multi-target interactions. This integrative strategy aims to advance the discovery of natural polypharmacological agents with enhanced therapeutic potential for hypertension management.

2 Materials and Methodology

2.1 Candidate proteins

Proteins involved in the Renin–Angiotensin System (RAS), Aldosterone Synthesis and Secretion (Aldo-SS), and Aldosterone-Regulated Sodium Reabsorption (ARSR) pathways—key regulatory mechanisms in hypertension—were selected as potential drug targets. Protein information and pathway details were retrieved from the Kyoto Encyclopedia of Genes and Genomes (KEGG) database (Kanehisa & Goto, 2000). In total, 76 proteins were included for analysis (Table s1).

2.2 Candidate compounds

Natural compounds with reported antihypertensive activity were selected from 17 medicinal plants, reported by Kamyab et al., (2021). The chemical structures of these 98 phytoconstituents were retrieved from the PubChem database in SDF format (Kim et al., 2016) for virtual screening and molecular docking (Table s2).

2.3 Computational resources

The following databases, tools, and web servers were used throughout the study: KEGG for pathway data (Kanehisa and Goto, 2000), STRING for protein–protein interaction network construction (Szklarczyk et al., 2021), Cytoscape for network visualization (Shannon et al., 2003), RCSB PDB for 3D structural data (Burley et al., 2017), OpenBabel for file conversion (O’Boyle et al., 2011), PockDrug Server for pocket druggability analysis (Hussain et al., 2015), AutoDock Tools and AutoDock Vina for docking and screening (Morris et al., 2009; Trott and Olson, 2010), and ADMETlab 2.0, for comprehensive ADMET property assessment (Xiong et al., 2021).

2.4 Identification of potential drug targets

Hypertension-associated pathways were extracted from KEGG, and corresponding proteins were analyzed. STRING-based protein–protein interaction networks (PPINs) were constructed, and Cytoscape was used to identify hub proteins based on node degree and betweenness centrality. High-resolution structures of selected proteins (≤ 3 Å) were retrieved from RCSB PDB, and PockDrug Server was employed to predict druggable pockets. Proteins with druggability scores ≥ 0.9 were considered high-confidence targets.

2.5 Ligand and receptor preparation and virtual screening

Natural compounds from PubChem were converted from SDF to PDBQT format using OpenBabel, while protein structures were processed using AutoDock Tools (Fig. 1). To scan entire protein for possible binding sites blind docking has been performed. Docking grid parameters were set to encompass the entire protein surface. Configuration files were generated for each protein–ligand complex. AutoDock Vina performed molecular docking under standard conditions (energy range = 10; exhaustiveness = 8). Compounds exhibiting binding energies of ≤ -8.0 kcal/mol and demonstrating significant interaction affinities with multiple target proteins were considered potential lead candidates for polypharmacological applications.

2.6 ADME analysis

The pharmacokinetic (ADME) profiles of all candidate compounds were predicted using ADMETlab 2.0, an integrated web-based platform for comprehensive ADMET property assessment (Xiong et al., 2021). The chemical structures of the docked compounds were converted into SMILES format and analyzed using the batch prediction module. Subsequently, all compounds were evaluated against four established drug-likeness filters, i.e., Lipinski’s Rule of Five (Lipinski et al., 2001), Pfizer and GSK 4/400 guidelines (Gleeson, 2008), and the Golden Triangle criteria (Waring, 2009). To ensure rigorous and reliable selection, only compounds

meeting at least three of these four criteria were considered potential candidates for further development.

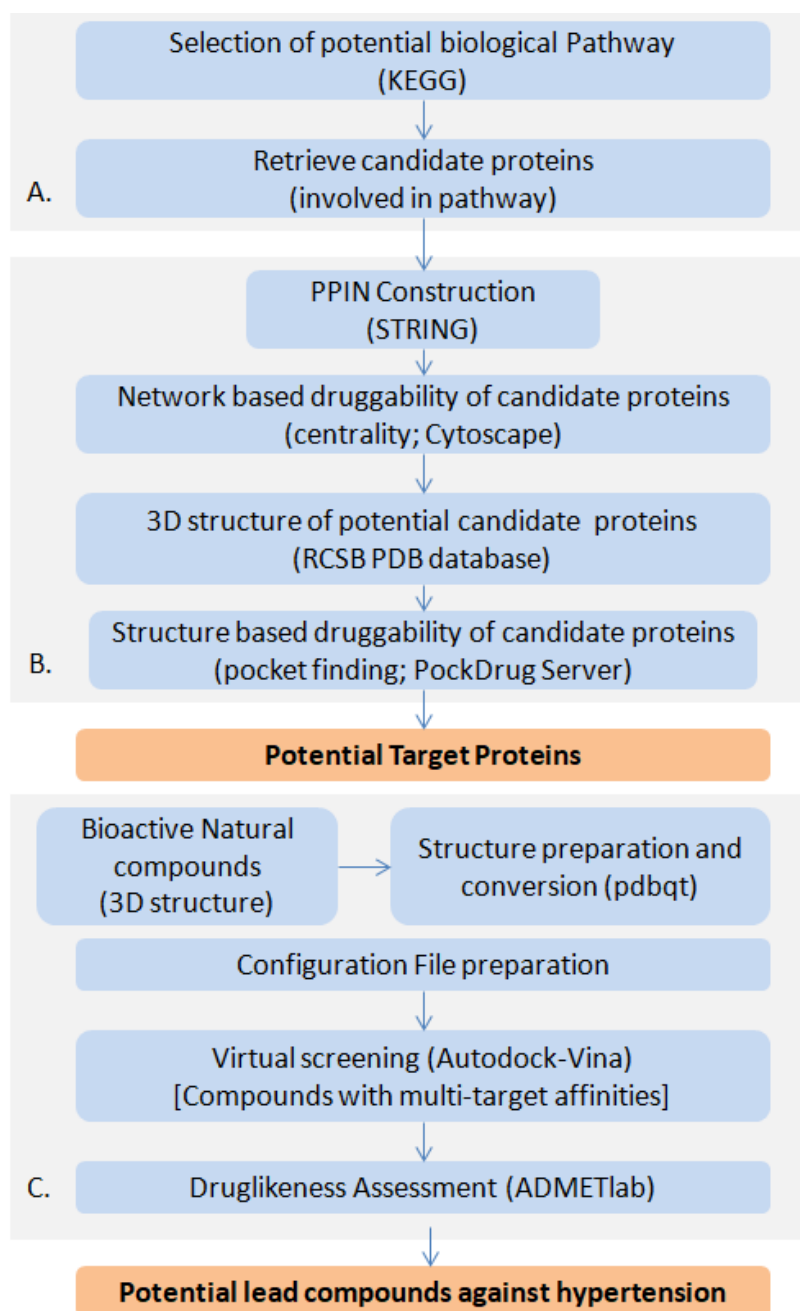


Fig. 1 Schematic representation of the integrative computational methodology used for target identification and compound screening.

3 Results and Discussion

3.1 Identification of candidate target proteins

3.1.1 Network-based druggability analysis

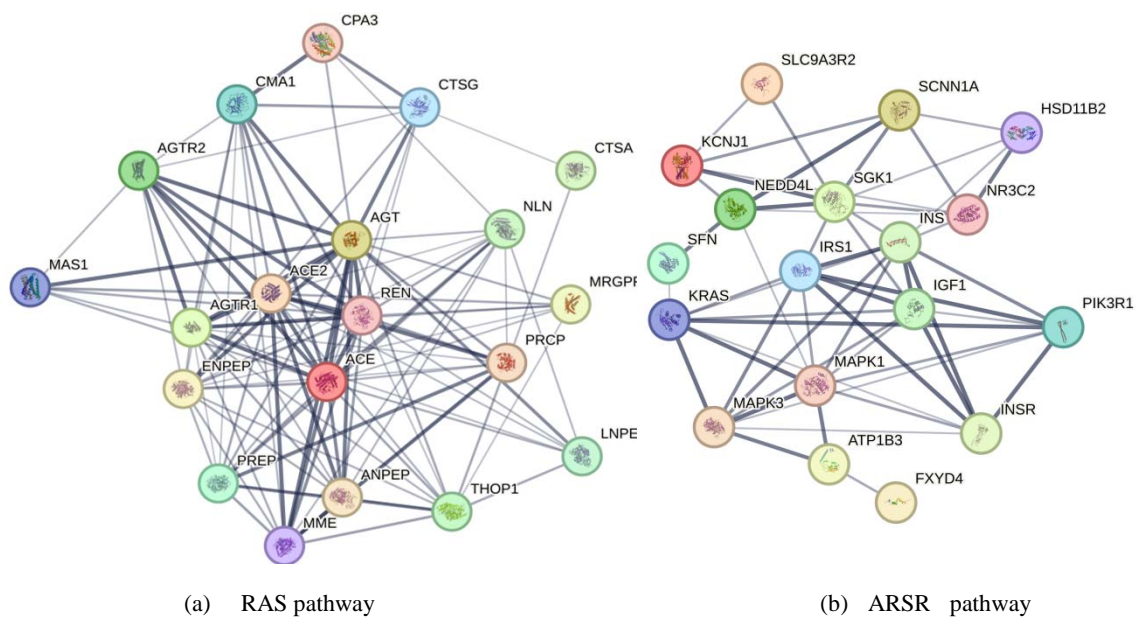
Three hypertension-associated pathways—the Renin–Angiotensin System (RAS), Aldosterone-Regulated Sodium Reabsorption, and Aldosterone Synthesis and Secretion—were retrieved from the KEGG database and analyzed to identify potential therapeutic targets. The proteins from these pathways were used as seed nodes to

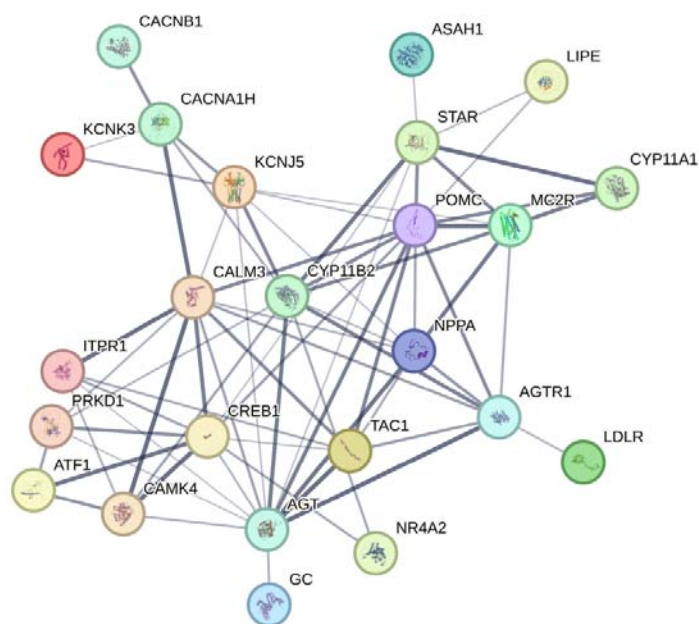
construct protein–protein interaction networks (PPINs) using the STRING database (Chen et al., 2019), followed by visualization and network topology analysis in Cytoscape. Key topological parameters such as node degree and betweenness centrality were used to assess the functional importance of each protein (Verma et al., 2020).

RAS Pathway: A total of 22 seed proteins were initially identified, forming a PPIN of 20 nodes and 112 edges after excluding the non-interacting protein NECTIN1 (Fig. 2a). The network exhibited a scale-free topology, consistent with biological networks where few nodes act as major hubs. Centrality analysis revealed AGT (angiotensinogen) as the most significant hub, followed by ACE, REN, ACE2, and ENPEP, underscoring their central roles in blood pressure regulation. The prominence of AGT and ACE correlates with their established pharmacological significance as core components of the RAS, frequently targeted by antihypertensive drugs such as ACE inhibitors and angiotensin receptor blockers (ARBs) (Kawai et al., 2017).

Aldosterone-Regulated Sodium Reabsorption Pathway: This network contained 18 nodes and 54 edges after removal of singleton nodes (CNKSR3, DBF4, DUSP2, and DNAH8). The INS and SGK1 proteins showed the highest degrees, suggesting key regulatory roles in sodium transport and blood pressure modulation (Fig. 2b). SGK1, in particular, is known to modulate epithelial sodium channels (ENaC) and contribute to renal sodium reabsorption (Lang et al., 2010). Other proteins, such as IRS1, IGF1, INSR, and PIK3CA, also showed significant degrees, reflecting their involvement in metabolic-hormonal cross-talk influencing cardiovascular regulation.

Aldosterone Synthesis and Secretion Pathway: The PPIN for this pathway, generated from 37 proteins, included 24 interacting nodes and 70 edges (Fig. 2c). AGT again emerged as a top hub (degree = 13), highlighting its multifunctional role across pathways. Additional key proteins such as POMC, CYP11B2, CALM3, and CREB1 were central to this network. Notably, CYP11B2, the gene encoding aldosterone synthase, plays a direct role in aldosterone biosynthesis and is a known genetic determinant in salt-sensitive hypertension (White, 2018).





(c) ALDO-SS pathway

Fig. 2 Protein-protein interaction networks (PPINs) of key proteins involved in hypertension-associated pathways: (a) Renin-Angiotensin System (RAS), (b) Aldosterone-Regulated Sodium Reabsorption (ARSR), and (c) Aldosterone Synthesis and Secretion (ALDO-SS) pathway.

Proteins with a node degree ≥ 10 were shortlisted as potential druggable targets (Table 1). The cross-pathway recurrence of AGT, ACE, and SGK1 reinforces their physiological significance and supports a systems-level approach to therapeutic targeting in hypertension.

Table 1 Candidate target proteins identified through PPI-network based druggability analysis (node with ≥ 10 degree).

S.N.	Pathway's	Protein's name with degree
1	RAS pathway (13)	AGT [18], ACE [17], REN [17], ACE2 [16], ENPEP [15], MME [12], ANPEP [12], PRCP [12], THOP1 [12], PREP [12], CMA1 [11], NLN [11], AGTR2 [10]
2	ARSR pathway (7)	INS [13], SGK1 [13], IRS1 [12], IGF1 [12], INSR [11], IRS2 [11], PIK3CA [11]
3	Aldo-SS pathway (5)	AGT [13], POMC [12], CYP11B2 [11], CALM3 [11], CREB1 [10]

3.1.2 Structure-based druggability analysis

Structure-based druggability analysis was conducted to identify proteins with suitable binding cavities for small-molecule interaction. High-resolution 3D protein structures were retrieved from the RCSB Protein Data Bank (PDB), prioritizing entries determined by X-ray crystallography or cryo-electron microscopy (≤ 3 Å).

Binding pocket analysis using the PockDrug Server revealed multiple druggable cavities with druggability scores ≥ 0.8 , indicative of favorable steric and physicochemical environments for ligand binding

(Table 2). Proteins such as ACE, AGT, CYP11B2, and SGK1 demonstrated particularly high druggability scores, validating their potential as viable targets for small-molecule modulation.

Table 2 Summary of target proteins and their predicted druggable features identified via structure-based analysis.

Pathway	S. N.	Protein	Druggability score	No. of pockets	PDB ID
RAS pathway	1	REN	0.9998557571	7	1BBS
	2	MME	0.934448871429	6	1DMT
	3	CMA1	0.9132915571	2	1KLT
	4	ACE	0.9387667	1	1O86
	5	ACE2	0.892952757143	3	1R42
	6	THOP1	0.9895933	4	1S4B
	7	PREP	0.9983725286	9	3DDU
	8	AGT	0.9985570857	13	3WOO
	9	ANPEP	0.9970315286	4	4FYQ
	10	ENPEP	0.9998765	6	4KXY
	11	NLN	0.9016696714	1	5LU2
ARSR Pathway	12	IRS1	0.9494322714	3	1K3A
	13	SGK1	0.977754	3	2R5T
	14	PIK3CA	0.9796438857	2	2V1Y
	15	INS	0.9945166	22	2WBY
	16	IRS2	0.9976187	2	3FQW
	17	INSR	0.9941109	14	6VEP
Aldo-SS pathway	18	CALM3	0.9992310429	2	1CLL
	19	AGT	0.9985570857	13	3WOO
	20	CYP11B2	0.9981829714	99	4DVQ
	21	POMC	0.9990387143	8	4XNH
	22	CREB1	0.9995165714	20	7TBH

3.2 Virtual screening and binding affinity analysis

Virtual screening using AutoDock Vina was performed to predict the interaction between selected target proteins and natural phytochemicals derived from 17 antihypertensive medicinal plants. Binding affinities (ΔG values in kcal/mol) served as indicators of interaction strength and complex stability.

Several natural compounds exhibited strong binding affinities (≤ -8.0 kcal/mol) with the predicted target proteins, and most of them showed affinity toward multiple target proteins across the three pathways. Few of these compounds, i.e., Ginsenoside Rb1 and 1-Deoxyforskolin have previously been reported to exhibit cardioprotective (Chen et al., 2019), vasodilatory, and anti-inflammatory effects, reinforcing their pharmacological potential against hypertension (Pan et al., 2012; Park et al., 2023; Pinto et al., 2008; Seifert et al., 2012).

3.3 Identification of potential lead compounds

Docking analyses across all pathways identified 22 natural compounds with significant binding affinities (≤ -8.0 kcal/mol). Among these, 16 compounds exhibited multi-target interactions, indicating potential polypharmacological activity. Polypharmacology offers particular advantages in addressing multifactorial disorders such as hypertension (Table 3). The ability of certain compounds to engage multiple targets underscores their potential to modulate interconnected physiological processes involved in blood pressure regulation, including vasoconstriction, renal sodium balance, and hormonal control.

Table 3 Predicted natural lead compounds with favorable drug-likeness profiles for potential hypertension therapy.

S.N.	Compound_id	Compound name	Lipinski	Pfizer	GSK	GT
1	14219439	1-Deoxyforskolin	A	A	A	A
2	14219442	7-Deacetyl-1-deoxyforskolin	A	A	A	A
3	13471717	9-Deoxyforskolin	A	A	A	A
4	709625	Cinnamoylglycine	A	A	A	A
5	969516	curcumin	A	A	A	A
6	5281855	ellagic acid	A	A	A	A
7	5280961	genistein	A	A	A	A
8	281377	Genistin	A	A	A	A
9	13673340	7-Deacetyl-1,9-dideoxyforskolin	A	R	A	A
10	107948	1,9-Dideoxyforskolin	A	R	A	A
Compounds with considerable affinity but poor druglikeness						
11	125001	10-Deacetyl baccatin III	A	A	R	R
12	14219437	9alpha-Hydroxy-8,13-Epoxy-Labd-14-En-11-One	A	R	R	A
13	10253669	Ginseng Tetrapeptide	R	A	R	R
14	9898279	Ginsenoside rb1	R	A	R	R
15	168356162	Andrographis paniculata	R	A	R	R
16	36314	Paclitaxel	R	A	R	R

A: Accepted, R: Rejected, GSK: GlaxoSmithKline, GT: GoldenTriangle.

3.4 Screening of compounds for drug-likeness and ADME properties

To assess the oral drug potential of the selected compounds, their physicochemical and pharmacokinetic (ADME) properties were evaluated. All 16 compounds were systematically screened against four well-established drug-likeness criteria: Lipinski's Rule of Five, Pfizer, GSK 4/400, and the Golden Triangle rules. These filters are widely recognized for predicting oral bioavailability and overall pharmacokinetic suitability (Lipinski et al., 2001; Gleeson, 2008; Waring, 2009). According to Lipinski's Rule of Five, compounds with molecular weight ≤ 500 Da, $\log P \leq 5$, and limited hydrogen bonding are likely to exhibit good oral bioavailability (Lipinski et

al., 2001). The Pfizer and GSK 4/400 rules further refine these parameters by emphasizing the effects of molecular weight and lipophilicity on ADME properties (Gleeson, 2008). The Golden Triangle model similarly balances molecular weight and log D to optimize absorption and clearance (Waring, 2009). For reliable selection, only compounds satisfying at least three of these four criteria were considered suitable for further development. This stringent multi-rule screening helped minimize false positives and ensured selection of chemically and pharmacokinetically viable candidates.

As a result, ten lead compounds (1-Deoxyforskolin; 7-Deacetyl-1-deoxyforskolin; 9-Deoxyforskolin, Cinnamoylglycine, curcumin; ellagic acid; genistein; Genistin; 7-Deacetyl-1,9-dideoxyforskolin; and 1,9-Dideoxyforskolin) demonstrated favorable drug-likeness and were shortlisted for subsequent analyses in table 3. Among the analyzed compounds, *Andrographis paniculata* (Okhuarobo et al. 2014), curcumin (Hadi et al. 2019), ellagic acid (Berkban et al. 2015), and genistein (Hemati, et al., 2020) have reported antihypertensive or vasoprotective effects in preclinical or clinical studies (Fig. 3).

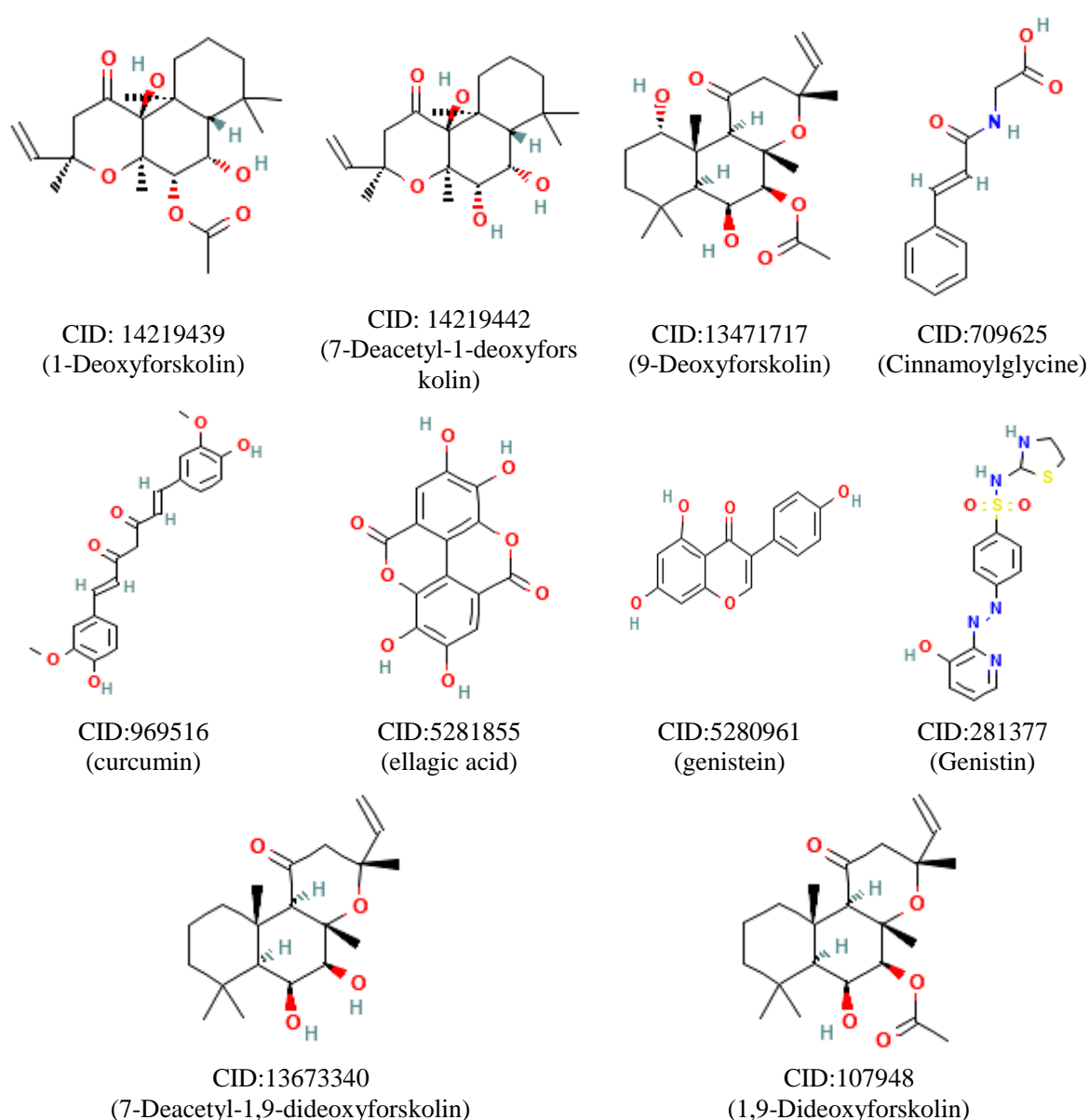


Fig. 3 Chemical structures (2D) of selected natural compounds exhibiting polypharmacological potential for hypertension management.

Although six compounds, i.e., 10-Deacetyl baccatin III; 9 α -Hydroxy-8,13-epoxy-labd-14-en-11-one; Ginseng tetrapeptide; Ginsenoside Rb1; Andrographis paniculata; and Paclitaxel—did not fully satisfy the established drug-likeness criteria (table 3), they should not be left over. Several of these molecules, particularly Ginsenoside Rb1, have been extensively reported for their cardioprotective, vasodilatory, and antihypertensive properties, indicating substantial pharmacological potential despite suboptimal physicochemical profiles (Pan et al., 2012; Park et al., 2023; Chen et al., 2019). Compounds such as paclitaxel and 10-deacetyl baccatin III also demonstrate noteworthy bioactivity and structural complexity, which may inspire analog development through rational modification. Therefore, quantitative structure–activity relationship (QSAR)-guided structural optimization is recommended to enhance the drug-likeness, bioavailability, and therapeutic suitability of these natural scaffolds for antihypertensive drug development.

3.5 Biological and therapeutic implications

This study demonstrates the utility of integrative network pharmacology and structure-based virtual screening for discovering natural bioactives targeting hypertension. The identification of recurrent hub proteins such as AGT, ACE, and SGK1 across multiple pathways underscores their central roles in cardiovascular regulation and validates their importance as potential drug targets. The convergence of computational predictions with reported pharmacological data enhances confidence in the identified targets and lead compounds. The multitarget interaction profiles of the screened natural molecules suggest their potential to achieve synergistic regulation of key hypertensive mechanisms, including vasoconstriction, sodium reabsorption, and hormonal modulation.

Considering the inherent low toxicity and high biocompatibility of natural compounds, these findings offer a promising foundation for the development of plant-derived polypharmacological antihypertensive agents. Nonetheless, further experimental validation—including molecular dynamics simulations and in vivo studies—is essential to substantiate the computational predictions and assess the clinical potential of these lead candidates.

4 Conclusions:

This study employs an integrative computational strategy that combines network pharmacology and structure-based virtual screening to identify natural compounds with potential antihypertensive activity. A total of twenty-two hypertension-associated protein targets were identified and virtual screening revealed sixteen phytochemicals with strong binding affinities, ten of which demonstrated favorable drug-likeness properties. The observed multi-target interactions suggest a potential for synergistic modulation of key hypertensive mechanisms through a polypharmacological mode of action. These findings underscore the promise of plant-derived molecules as safer and more biocompatible alternatives to conventional antihypertensive agents. Nevertheless, comprehensive validation through molecular dynamics simulations, in vitro assays, and in vivo studies is required to substantiate their pharmacological efficacy and clinical applicability.

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Supplementary Data

Table s1 Selected proteins from hypertension-related pathways.

SN	Protein	Protein ID	Gene ID	Uniprot ID
A.	RAS pathway			
1	ACE	NP_000780	1636	P12821
2	ACE2	NP_068576	59272	Q9BYF1
3	AGT	NP_001369746	183	-NA-
4	AGTR1	NP_000676	185	P30556
5	AGTR2	NP_031455	186	P35374
6	PREP	NP_002717	5550	P48147
7	CMA1	NP_001827	1215	P23946
8	CTSG	NP_001902	1511	P08311
9	MAS1	NP_002368	4142	P04201
10	MME	NP_000893	4311	P08473
11	REN	NP_000528	5972	P00797
12	Tonin	NP_002248	3816	P06870
13	CPA3	NP_001861	1359	P15088
14	PRCP	NP_005031	5547	P42785
15	AP-N	NP_001141	290	P15144
16	AP-A	NP_001968	2028	Q07075
17	MRGPRD	NP_944605	116512	Q8TDS7
18	PRR	NP_005756	10159	O75787
19	CTSA	NP_000299	5476	P10619
20	NLN	NP_065777	57486	Q9B4T8
21	THOP1	NP_003240	7064	P52888
22	IRAP	NP_005566	4012	Q9UIQ6
B	Aldosterone-Regulated Sodium Reabsorptions pathway			
1	RoMK	NP_000211	3758	P48048
2	NHERF2	NP_001123484	9351	Q15599
3	EnaC	NP_001029	6337	P37088
4	SGK1	NP_005618	6446	O00141
5	Nedd4-2	NP_001138439	23327	Q96PU5
6	143-3	NP_006133	2810	P31947
7	PI3K	NP_852664	5295	P27986
8	IRS1	NP_005535	3667	P35568
9	k_ras2	NP_203524	3845	P01116
10	11 β -HSD2	NP_000187	3291	P80365
11	MR	NP_000892	4306	P08235
12	ERK1/2	NP_002736	5594	P28482
	ERK1/2	NP_002737	5595	P27361
13	CHIF	NP_001171892	53828	P59646
14	ATPase	NP_001670	483	P54709

15	IR	NP_000199	3643	P06213
16	Insulin	NP_000198	3630	P01308
17	IGF	NP_001104755	3479	P05019
C.	Aldosterone Synthesis and Secretion pathway			
1	TASK	NP_002237	3777	O14649
2	KCNJ5	NP_000881	3762	P48544
3	NKA	NP_001670	483	P54709
4	SOC	NP_116179	84876	Q96D31
5	PMCA	NP_001673	490	P20020
6	LDLR	NP_00518	3949	P01130
7	SR-B1	NP_005496	949	Q8WTV0
8	MC2R	NP_000520	4158	Q01718
9	AC	NP_066939	107	Q08828
10	GC	NP_000897	4881	P16066
11	ANF	NP_006163	4878	P01160
12	ACTH	NP_000930	5443	P01189
13	Gq/11	NP_002063	2776	P50148
14	PLC β	NP_056007	23236	Q9NQ66
15	IP3R	NP_002214	3709	Q14571
16	PKC	NP_997700	5579	P05771
17	PKD	NP_001073349	27565	Q9BZL6
18	DAGL	NP_631918	221955	QBNCG7
19	CaM	NP_001734	805	P0DP23
20	CaMK	NP_003647	8536	Q14012
21	CREB	NP_004370	1383	P16220
22	ATF1	NP_005162	466	P18846
23	HSL	NP_0053448	3991	Q05469
24	NURR1	NP_006177	4929	P43354
25	NGF1B	NP_002126	3164	P22736
26	StAR	NP_000340	6770	P49675
27	CyP21A	NP_000491	1589	P08686
28	3 β -HSD	NP_000853	3283	P14060
29	CyP11A1	NP_000772	1583	P05108
30	PKA	NP_002721	5566	P17612
31	PDE2	NP_002590	5138	O00408
32	GS	NP_000507	2778	P63092
33	CyP11B2	NP_000489	1585	P19099
34	T-type	NP_061496	8913	O43497
35	L-type	NP_955630	775	Q13936
36	AGT	NP_001369746	183	-NA-
37	AGTR1	NP_000676	185	P30556

Table s2 List of natural compounds with their PubChem ID and Molecular Formula considered for screening.

S.N.	Compound ID	Molecular Formula	Compounds Name
<i>Tribulus terrestris</i>			
1	CID:604	C6H12O7	Hexonic acid
2	CID:586	C4H9N3O2	creatine
<i>Rauwolfia serpentina</i>			
3	CID:5770	C33H40N2O9	Reserpine
<i>Coleus forskohlii</i>			
4	CID:47936	C22H34O7	forskolin
5	CID:107948	C22H34O5	1,9-Dideoxyforskolin
6	CID: 10044542	C20H32O6	Deacetylforskolin
7	CID: 13471717	C22H34O6	9-Deoxyforskolin
8	CID: 14219439	C22H34O6	1-Deoxyforskolin
9	CID: 14219437	C20H32O3	9alpha-Hydroxy-8,13-Epoxy-Labd-14-En-11-One
10	CID: 13673340	C20H32O4	7-Deacetyl-1,9-dideoxyforskolin
11	CID: 14219442	C20H32O5	7-Deacetyl-1-deoxyforskolin
<i>Sesamum indicum</i>			
12	CID: 131801617	C ₂₀ H ₁₈ O ₇	Sesamolin
<i>Camellia sinensis</i>			
13	CID: 168009904	C80H154N4O6S2	Camellia Sinensis Leaf Oil
<i>Curcuma longa</i>			
14	CID: 969516	C21H20O6	curcumin
<i>Glycine max</i>			
15	CID: 750	C2H5NO2	glycine
16	CID: 5280961	C15H10O5	genistein
17	CID: 3496	C3H8NO5P	glyphosate
18	CID: 6049	C10H16N2O8	Edetic acid
19	CID: 464	C9H9NO3	Hippuric acid
20	CID: 1088	C3H7NO2	sarcosine
21	CID: 974	C2H3NO3	OXAMIC ACID
22	CID: 5281377	C21H20O10	Genistin
23	CID: 673	C4H9NO2	N, N-dimethylglycine
24	CID: 10253	C9H9NO4	Salicyluric acid
25	CID: 10972	C4H7NO3	N-Acetylglycine
26	CID: 8897	C4H7NO4	Iminodiacetic Acid
27	CID: 439498	C5H10N2O3S	Cysteinylglycine
28	CID: 11163	C4H8N2O3	Glycylglycine
29	CID: 68499	C8H8N2O3	Nicotinuric acid
30	CID: 3866	C8H9NO2	2-Amino-2-phenylaceticacid
31	CID: 7152	C6H11NO5	N-(2-Hydroxyethyl) iminodiacetic acid
32	CID: 70910	C10H19N3O4	Leucyl-glycyl-glycine
33	CID: 709625	C11H11NO3	Cinnamoylglycine

34	CID: 6426709	C7H12N2O3	L-Prolylglycine
35	CID: 185909	C5H7NO2	Propargylglycine
36	CID: 23716553	C3H7KNO5P	Glyphosate potassium
37	CID: 83228	C6H14N2O3	Lysine, 5-hydroxy-
38	CID: 2232523	C11H11NO3	Glycine, N-cinnamoyl-, Z-
H	<i>Andrographis paniculata</i>		
39	CID: 168356162	C68H42O8S8	Andrographis paniculata
I	<i>Taxus brevifolia</i>		
40	CID: 36314	C47H51NO14	Paclitaxel
41	CID: 125001	C29H36O10	10-Deacetyl baccatin III
J	<i>Ephedra sinica</i>		
42	CID: 9294	C10H15NO	Ephedrine
43	CID: 7028	C10H15NO	PSEUDOEPHEDRINE
44	CID: 3007	C9H13N	AMPHETAMINE
45	CID: 10297	C9H13NO	phenylpropanolamine
46	CID: 441457	C9H13NO	Cathine
47	CID: 162265	C9H13NO	Norpseudoephedrine
48	CID: 5032	C10H15NO	racedrine
49	CID: 64782	C11H17NO	(1R,2S)-2-(dimethylamino)-1-phenylpropan-1-ol
50	CID: 1206	C10H15N	DL-Methamphetamine
51	CID: 4374	C11H17NO	Methylephedrine
52	CID: 62946	C10H15NO	(-)-Pseudoephedrine
53	CID: 71290	C10H16ClNO	(1S,2R) -(+)-Ephedrine hydrochloride
54	CID: 7059596	C11H17NO	(+)-N-Methylpseudoephedrine
55	CID: 12776702	C10H16N2O	n-amino-1-ephedrine
56	CID: 9920426	C9H10O2	(R)-1-Hydroxy-1-phenylacetone
57	CID: 27869	C12H17NO2	N-(1-hydroxy-1-phenylpropan-2-yl)-N-methylacetamide
58	CID: 5282591	C10H15NO2	Ephedrine, m-hydroxy-
59	CID: 5354526	C10H14N2O2	N-[(1R,2S)-1-hydroxy-1-phenylpropan-2-yl]-N-methylnitrous amide
60	CID: 71291	C12H17NO2	[(1R,2S)-2-(methylamino)-1-phenylpropyl] acetate
61	CID: 67242163	C20H32N2O3	Ephedrine hemihydrate
62	CID: 528872	C15H22F3NO2Si	Ephedrine, N-TFA-O-TMS
63	CID: 3808691	C11H17NO	ephedrine methyl ether
64	CID: 71294	C10H16ClNS	1-Propanethiol, 2-(methylamino)-1-phenyl-, hydrochloride
65	CID: 6710657	C10H15NO	(1R)-2-(methylamino)-1-phenyl-1-propanol
66	CID: 69340856	C11H18ClNO	2-(Ethylamino)-1-Phenylpropan-1-ol Hydrochloride
67	CID: 71287	C10H16NO4P	2-(methylamino)-1-phenylpropyl dihydrogen phosphate
68	CID: 68632441	C13H19NO	2,2,3,4-Tetramethyl-5-phenyl-1,3-oxazolidine
69	CID: 582495	C16H31NOSi2	Ephedrine di-TMS
70	CID: 25021608	C15H21NO3	Ephedrine levulinate
71	CID: 16213493	C10H16ClNO	(1R,2S) -(-)-Ephedrine-d3 Hydrochloride

72	CID: 91724239	C17H21F3N2O3	Ephedrine-TPC Derivative
73	CID: 547373	C12H17NO2	Ephedrine acetate
74	CID: 91735712	C18H28F3NO2Si	Ephedrine, N-trifluoroacetyl-O-(t.-butyl) dimethylsilyl-
75	CID: 6420918	C14H21NO3	Ephedrine, N-propyloxycarbonyl-
76	CID: 71293	C10H16NO4P	L-alpha-(1-(Methylamino)ethyl)benzyl phosphate
77	CID: 44150471	C20H30Cl2N2S2	Beta, beta'-Dithiobis(N,alphadimethylphenethylamine) dihydrochloride
78	CID: 71292	C10H16NO4P	D-alpha-(1- (Methylamino ethyl) benzyl phosphate
79	CID: 16213497	C10H16ClNO	(1s,2s) -(+)-Pseudoephedrine-D3 Hcl (N-Methyl-D3)
80	CID: 38091	C14H19NO2	(-)-N-(beta-Hydroxy-alpha-methylphenethyl)-N-methylmethacrylamide
81	CID: 12625680	C10H16ClNO2	Oxilofrine hydrochloride
K	<i>Salix alba</i>		
82	CID: 2244	C9H8O4	aspirin
L	<i>Castanospermum austral</i>		
83	CID: 54445	C8H15NO4	castanospermine
84	CID: 24721273	C8H16ClNO4	Australine HCl
85	CID: 53398646	C8H16ClNO4	Australine Hydrochloride
M	<i>Panax ginseng</i>		
86	CID: 9898279	C54H92O23	Ginsenoside rb1
87	CID: 10253669	C18H33N7O7	Ginseng Tetrapeptide
N	<i>Onion cepa</i>		
88	CID: 12890356	C7H16ClNO2	methyl 2-amino-3-methylpentanoate hydrochloride
O	<i>Zingiber officinale</i>		
89	CID: 702	C2H6O	ethanol
90	CID: 338	C7H6O3	salicylic acid
91	CID: 442793	C17H26O4	gingerol
92	CID: 5281794	C17H24O3	Shogaol
93	CID: 92776	C15H24	Zingiberene
94	CID: 11369949	C17H28O4	Gingerdiol
95	CID: 162952	C17H24O4	Gingerdione
P	<i>Punica granatum</i>		
96	CID: 5281855	C14H6O8	ellagic acid
Q	<i>Allium sativum</i>		
97	CID: 65036	C6H10OS2	Allicin
98	CID: 9793905	C6H11NO2S	S-Allylcysteine