Дослідження

Research

НИРКИ KIDNEYS

DOI: 10.65327/kidneys.v15i1.600

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Analysing potential phytoconstituents from *Viscum album* (Suvarnabandaaka) targeting RAAS-mediated hypertension and renal protection: An *in-silico* approach

For citation: Kideys. 2026;15(1): 72-81. Acceptance- 15/01/2026
Received- 17/11/2025 Doi: 10.65327/kidneys.v15i1.600

Abstract

Background and Aim: Hypertension is a significant health issue in the world that demands that natural options to synthetic drugs should be explored because of their side effects. One of the key causes of chronic kidney disease (CKD) is hypertension, which mainly causes dysregulation of renal RAAS signalling and vascular injury. This paper examines the antihypertensive effects of *Viscum album* by using *in-silico* molecular docking.

Material and Methods: Phytoconstituents of *Viscum album* were identified using seven phytoconstituents based on the scores of their oral bioavailability and drug-likeness. AutoDock 4.5.6 molecular docking was done against the following key hypertensive targets: ACE, Angiotensin-II receptor, β-1 adrenergic receptor, and calcium channel. Biovia Discovery Studio was used to visualise the interactions. **Result:** The phytoconstituents had better binding affinities with the target proteins than the standard drugs. It was worth noting that Chlorogenic acid, Oleanolic acid and Betulinic acid displayed a high interaction with ACE as the binding energy of the substance was -11.90, -11.84 and -11.65 kcal/mol, which exceeded that of Captopril of -5.89 kcal/mol. In the case of the Angiotensin-II receptor, Oleanolic acid, Chlorogenic acid, and Syringin demonstrated binding energies of -11.66, -10.67 and -10.05 kcal/mol, outperforming losartan's -9.21 kcal/mol. Syringin, Chlorogenic acid, and Quercetin exhibited robust binding with the β-1 adrenergic receptor, with energies of -13.82, 13.59, and -12.05 kcal/mol, respectively, compared to Propranolol's -7.48 kcal/mol. Additionally,
Chlorogenic acid, Oleanolic acid, and Quercetin interacted strongly with the calcium channel, with binding energies of -7.24, -7.06, and -7.00 kcal/mol, respectively, exceeding amlodipine's -4.59 kcal/mol.

Conclusion: Such results indicate that *Viscum album* phytoconstituents can have a dual antihypertensive and nephroprotective action of regulating major renal targets.

Keywords: *Viscum album*, Suvarnabandaaka, Hypertension, *In-silico*, Molecular docking, Phytoconstituents

1. Introduction

Hypertension or high blood pressure is a long-term health problem that is defined by the continuous increase in blood pressure in the arteries [1]. This ailment is also very dangerous in terms of health, given that it has some dire consequences like heart disease, stroke and kidney failure [2]. The World Health Organisation (WHO) indicates that more than a billion individuals in the world

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are victims of hypertension, most of whom do not know that they are suffering as a result of high blood pressure [3]. The unhealthy lifestyle habits, which lead to hypertension, are high levels of salt intake, obesity, lack of physical activity, and tobacco consumption. Also, hereditary factors and age are critical factors contributing to the occurrence of this condition [2]. Hypertension is a serious health condition that needs to be managed properly to minimise morbidity and mortality due to cardiovascular diseases.

Hypertension is considered to be one of the most common causes of chronic kidney disease (CKD) and end-stage renal disease globally. Low initial and continuous rise in blood pressure causes structural and functional injury of renal vasculature, glomeruli, and tubulointerstitial compartments, which results in progressive nephron loss [4]. The kidney is the key factor in the regulation of blood pressure via the renin-angiotensin-aldosterone system (RAAS), the activity of the sympathetic nervous system, and the regulation of vascular tone by the actions of calcium. The dysregulation of these pathways not only causes consequences of increased blood pressure and decrease the risk of cardiovascular disease. Notably, these molecular targets are highly up-regulated in the renal tissues and are essential in the regulation of glomerular hemodynamics, sodium-water balance, and renin discharge. Direct effects include an aberrant activation of ACE, angiotensin II receptor, β-adrenergic receptor and calcium channels, which are clinically pertinent targets in the management of renal disease [5].

Existing pharmaceutical approaches for mitigating hypertension and renal disease progression encompass various drugs. These drugs are effective but show a variety of adverse effects. Captopril, Losartan, Propranolol and Amlodipine are utilised to manage hypertension, but can cause serious side effects. Captopril, an ACE inhibitor, may lead to angioedema (swelling of the face, lips, or tongue) [10], neutropenia (increased infection risk with symptoms like fever) [11], kidney damage (reduced urine output, swelling), hypotension (dizziness, fainting), hyperkalemia (muscle weakness), and liver damage [12]. Losartan, an angiotensin-II receptor antagonist, may lead to hypotension (dizziness, fainting) [13], kidney damage (reduced urine output) [14], hyperkalemia (life-threatening muscle weakness) [15], and severe allergic reactions (swelling, breathing difficulties) [16]. Propranolol, a beta-blocker, can cause serious side effects such as allergic reactions (swelling, breathing difficulties) [16], heart problems (bradycardia, heart block), breathing issues (bronchospasm) [17] and low blood sugar (masking hypoglycemia symptoms) [18]. Amlodipine, a calcium channel blocker, may lead to hypotension (dizziness, fainting) [19], edema (swelling) [20], and severe allergic reactions [21]. This emphasises the necessity for drug development focused on medication with negligible adverse effects. Consequently, herbal remedies, with their diverse pharmacological activities and generally safer profiles, offer promising alternatives.

systemic hypertension but also hastens renal inflammatory, fibrotic and proteinuric changes [5].

Pathophysiology of hypertension is a process that is associated with a number of important proteins that control vascular tone and blood pressure. Angiotensin-converting enzyme (ACE) is an important part of the renin-angiotensin-aldosterone system (RAAS), which converts angiotensin I into angiotensin II, a powerful vasoconstrictor that raises blood pressure considerably [6]. Angiotensin II receptor (AT-1 receptor) is the receptor that facilitates the action of angiotensin II to enhance vasoconstriction and sodium reabsorption, which increases the levels of blood pressure [7]. The main effect of the β-1 adrenergic receptor is on heart functioning; its stimulation causes an acceleration of the heart rate and contractility, which translates into an increase in cardiac output and blood pressure [8]. Vascular smooth muscles contract through calcium channels, which aid in the contraction process by performing the process of calcium influx, leading to vasoconstriction [9]. Taken together, these proteins constitute important antihypertensive effectors of antihypertensive therapy that can limit the

Viscum album has been used in traditional medicine for centuries because of its various pharmacological actions: it can act as a vasodilator, cardiac depressant, etc. [22]. There is a wide variety of bioactive compounds in the plant, including lectin, flavonoids, triterpenes and alkaloids, which have a therapeutic effect on the plant under different mechanisms, including anti-inflammatory and diuretic activity [22]. The research objective here is to determine the molecular interactions of the phytoconstituents of *Viscum album* (Suvarnabandaaka) and commercial drugs in the presence of major protein targets related to the development of hypertension and renal diseases. The given approach can not only give some insight into the possible mechanism of the antihypertensive action of *Viscum album* but also contribute to the introduction of traditional herbal remedies into the current treatment of hypertension and the management of renal disease progression. The purpose of the study is to find possible therapeutic agents that have fewer side effects than the existing standard drugs that are used in the treatment of hypertension and progression of renal diseases. This strategy can result in the emergence of new, safer therapeutic agents of plant origin.

2. Materials and Method

2.1. Data Collection: An exhaustive literature review was performed to determine the active components of *Viscum album* and filtered with the criteria of drug-likeness (≥0.18) and oral bioavailability (≥30%) scores.

2.2. Structure Retrievals: The three-dimensional structures of selected phytochemicals were retrieved from the PubChem database (https://pubchem.ncbi.nlm.nih.gov). Additionally, the 3D structure of selected target proteins, including ACE (PDB ID: 108A), Angiotensin-II receptor (PDB ID: 6JOD), β-1-adrenergic receptor (PDB ID: 7BU6), Calcium Channel (PDB ID: 8FD7), were obtained from Protein Data Bank (PDB) (https://www.rcsb.org) [23].

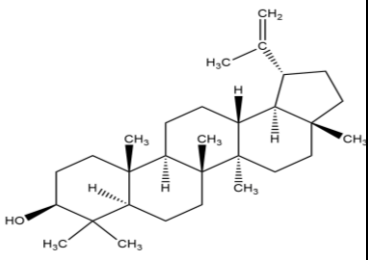
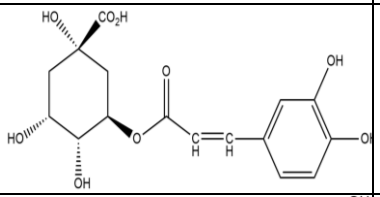
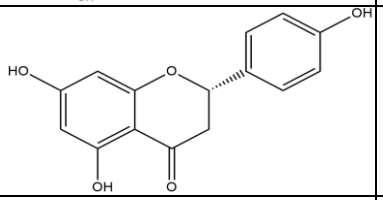
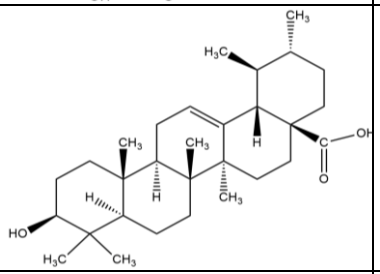
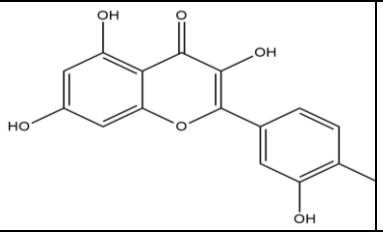
2.3. ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) and Drug-related Properties: The Swiss ADME tool (http://www.swissadme.ch) was utilised to assess the drug likeness, bioavailability scores and ADME (Absorption, Distribution, Metabolism, and Excretion) profiles of phytochemicals [24]. For toxicity estimation of the phyto-compounds, the ProTox-II web server (https://tox-new.charite.de/protox_II) was employed [25].

2.4. Molecular docking analysis: The configurational optimisation of selected phytochemicals was performed by the Avogadro tool (https://avogadro.cc) [26]. Interaction studies between target proteins with selected ligands were carried out with AutoDock 4.2 and AutoDock Tools 1.5.6 (http://www.scripps.edu/mb/olson/doc/autodock). This process began with protein preparation, which involved removing water molecules, existing ligands, and heteroatoms using UCSF Chimera [27]. The prepared proteins were then loaded into AutoDock Tool (v1.5.6), where polar hydrogens and Kollman charges were added, followed by assigning AD4 type. The grid box for docking was centred and its dimensions adjusted using the DeepSite tool (https://www.playmolecule.com/deepsite). Docking studies evaluated how the selected phytochemicals interacted with target proteins, and the resulting docked structures were visualised using Biovia Discovery Studio to analyse both 2D & 3D binding interactions.

3. Results

3.1. Screening of phytochemicals and Potential targets: Herbal components were identified through an extensive literature review. The bioactive compounds were screened based on their drug-likeness (≥0.18) and oral bioavailability (≥30%) scores. This screening process resulted in the selection of seven active compounds for further detailed analysis (Table 1), which included assessment of drug likeness (as depicted in Table 2), ADME (as shown in Table 3), Toxicity properties (as illustrated in Table 4) and molecular docking studies.

Table 1. Structure, Chemical Name, and Formula of Ligands

Ligands	Structure	Chemical Name	Chemical Formula
Betulinic acid		(1R,3aR,5aR,5bR,7aR,9S,11aR,11bR,13aR,13bR)-3a,5a,5b,8,8,11a-hexamethyl-1-(prop-1-en-2-yl)icosahydro-1H-cyclopenta[a]chrysen-9-ol	$C_{30}H_{50}O$
Chlorogenic acid		(1S,3R,4R,5R)-3-((3-(3,4-dihydroxyphenyl)acryloyl)oxy)-1,4,5-trihydroxycyclohexanecarboxylic acid	$C_{16}H_{18}O_9$
Naringenin		(S)-5,7-dihydroxy-2-(4-hydroxyphenyl)chroman-4-one	$C_{15}H_{12}O_5$
Oleanolic acid		(1S,2R,4aS,6aS,6bR,8aR,10S,12aR,12bR,14bS)-10-hydroxy-1,2,6a,6b,9,9,12a-heptamethyl-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-icosahydropicene-4a-carboxylic acid	$C_{30}H_{48}O_3$
Quercetin		3,5,7-trihydroxy-2-(3-hydroxy-4-methylphenyl)-4H-chromen-4-one	$C_{16}H_{12}O_6$

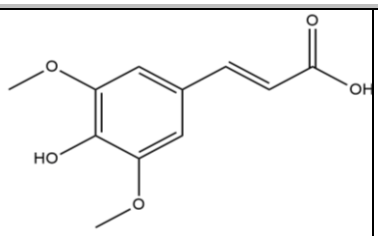
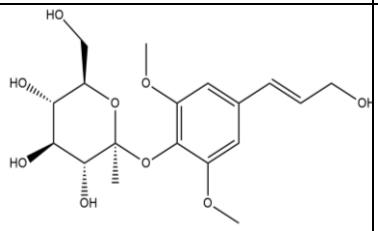
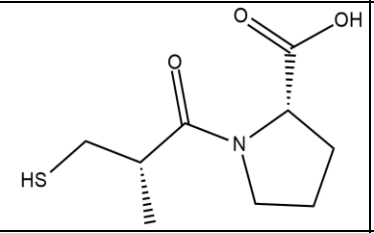
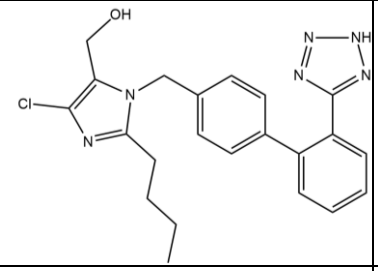
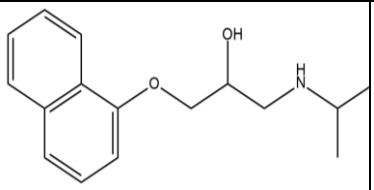
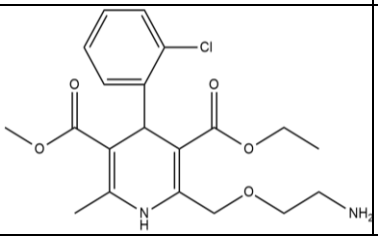
Sinapic acid		(E)-3-(4-hydroxy-3,5-dimethoxyphenyl)acrylic acid	$C_{11}H_{12}O_5$
Syringin		(2S,3R,4S,5S,6R)-6-(hydroxymethyl)-2-(4-((E)-3-hydroxyprop-1-en-1-yl)-2,6-dimethoxyphenoxy)-2-methyltetrahydro-2H-pyran-3,4,5-triol	$C_{18}H_{26}O_9$
Captopril		(S)-1-((S)-3-mercapto-2-methylpropanoyl)pyrrolidine-2-carboxylic acid	$C_9H_{15}NO_3S$
Losartan		(1-((2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-2-butyl-4-chloro-1H-imidazol-5-yl)methanol	$C_{22}H_{23}ClN_6O$
Propranolol		1-(isopropylamino)-3-(naphthalen-1-yloxy)propan-2-ol	$C_{16}H_{21}NO_2$
Amlodipine		3-ethyl 5-methyl 2-((2-aminoethoxy)methyl)-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate	$C_{20}H_{25}ClN_2O_5$

Table 2. Drug likeness of phytoconstituents of *Viscum album* and standard drugs

Phytochemicals	Molecular weight	Log p	HBD	HBA	Molar refractivity	No. of violation	BS
Betulinic acid	456.7	8.2	2	3	136.91	1	0.85
Chlorogenic acid	354.3	-0.4	6	9	83.50	1	0.11
Naringenin	272.2	2.4	3	5	71.57	0	0.55
Oleanolic acid	456.7	7.5	2	3	136.65	1	0.85
Quercetin	302.2	1.5	5	7	78.03	0	0.55
Sinapic acid	224.2	1.5	2	5	58.12	0	0.56
Syringin	372.4	-1.3	5	9	89.23	0	0.55
Captopril	217.29	0.3	2	4	59.97	0	0.56
Losartan	422.9	4.3	2	5	117.11	0	0.56
Propranolol	259.34	3	2	3	78.44	0	0.55
Amlodipine	408.9	3	2	7	108.93	0	0.55

Table 3. ADME properties of phytoconstituents of *Viscum album* and standard drugs

Phytochemicals	GIA	BBB	CYPIA2	CYP2C19	CYP2C9	CYP2D6	CYP3A4

Betulinic acid	Low	No	No	No	Yes	No	No
Chlorogenic acid	Low	No	No	No	No	No	No
Naringenin	High	No	Yes	No	No	No	Yes
Oleanolic acid	Low	No	No	No	No	No	No
Quercetin	High	No	Yes	No	No	Yes	Yes
Sinapic acid	High	No	No	No	No	No	No
Syringin	Low	No	No	No	No	No	No
Captopril	High	No	No	No	No	No	No
Losartan	High	No	No	Yes	Yes	Yes	Yes
Propranolol	High	No	Yes	No	No	Yes	No
Amlodipine	High	No	Yes	Yes	Yes	No	Yes

Table 4. Toxicity properties of phytoconstituents of *Viscum album* and standard drugs

Phytochemicals	LD50 (mg/kg)	Mutagenicity	Carcinogenicity	Hepatotoxicity
Betulinic acid	2610	Inactive	Active	Inactive
Chlorogenic acid	5000	Inactive	Inactive	Inactive
Naringenin	2000	Inactive	Inactive	Inactive
Oleanolic acid	2000	Inactive	Inactive	Inactive
Quercetin	159	Inactive	Active	Inactive
Sinapic acid	1772	Inactive	Inactive	Inactive
Syringin	4000	Inactive	Active	Inactive
Captopril	2078	Inactive	Active	Inactive
Losartan	300	Active	Inactive	Inactive
Propranolol	105	Inactive	Inactive	Inactive
Amlodipine	37	Inactive	Inactive	Inactive

3.2. Molecular Docking: Docking analyses were carried out to examine the interaction between phytoconstituents and hypertension-related and renal disease progression-related targets through AutoDock version 4.5.6. The main aim of the analysis was to determine the most favourable binding conformations because a negative binding energy implied a greater binding affinity. Namely, a binding energy lower than 0 kcal/mol indicates favourable interactions between phytochemicals and their targets. The visual expression of the optimal docking pose was presented both in 2D and 3D forms, as shown in Figure 1.

The binding affinities less than -6 kcal/mol of phyto-compound to the target are an indication of a strong binding interaction. The binding interaction and the inhibition constant of different compounds and their amino acid residues with specific targets have been widely examined, as represented in Table 5. Phytoconstituents have shown a great binding interaction with the target proteins, and in many cases, it is better than that of the standard drugs. For instance, Chlorogenic acid, Oleanolic acid, and Betulinic acid exhibited high binding interactions with ACE, at -11.90, -11.84, and -11.84 kcal/mol, respectively, compared to Captopril's lower affinity of -5.89 kcal/mol. Similarly, Oleanolic acid, Chlorogenic acid, and Syringin exhibited strong binding energies with the Angiotensin-II receptor, at -11.66, -10.67, and -10.34 kcal/mol, respectively, outperforming Losartan's affinity of -9.21 kcal/mol. Additionally, Syringin, Chlorogenic acid, Quercetin, and Naringenin exhibited robust binding interactions with β-1 adrenergic receptor, with affinities of -13.82, -13.59, -12.05, and -11.03 kcal/mol, respectively, compared to Propranolol's affinity of -7.48 kcal/mol. Lastly, Chlorogenic acid, Oleanolic acid and Quercetin demonstrated high binding energies with Calcium Channel, at -7.24, -7.06, and -7.00 kcal/mol, respectively, while Amlodipine showed a lower affinity of -4.59 kcal/mol. These results demonstrate the perspectives of phytoconstituents as promising therapeutic agents.

Table 5. Binding affinity between Ligands and Target Proteins

Target Proteins	Phytochemicals	Binding affinity (Kcal/mol)	Inhibition constant	Amino acid residues	No. of H-bonds
Angiotensin Converting Enzyme	Betulinic acid	-11.65	2.89 nM	**GLU A:411**, HIS A:410, HIS A:387, PHE A:391, TRP A:59, TYR A:360, TYR A:62, ALA A:63	1
	Chlorogenic acid	-11.90	1.89 nM	**ALA :366, ASP A:358**, ASN A:70, SER A:516, TRP A:357	4
	Naringenin	-10.04	44.06 nM	**LYS A:368, ASN A:70, SER A:516, GLU A:411, HIS A:383**, GLU A:384, PHE A:512	5
	Oleanolic acid	-11.84	2.09 nM	**ASN A:66, GLU A: 411**, HIS A:387, VAL A:518, LEU A:139, PHE A:512	2

	Quercetin	-10.96	9.26 nM	**ASN A:70, SER A:355, ALA A:356, ASP A:358**, TRP A:357, ALA A:63	4
	Sinapic acid	-8.32	793.60 nM	**ASN A:66, SER A:355, ASP A:358, ASN A:70**, TRP A:357, TYR A:62, PHE A:391, LYS A:368	4
	Syringin	-10.69	14.53 nM	**ASN A:70, ASP A:358, ARG A:402**, TRP A:357, ALA A:63	3
	Captopril	-5.89	47.83 uM	**GLU A:411, ARG A:522, TYR A:523, HIS A:383,** HIS A:387	4
Angiotensin II Receptor	Betulinic acid	-9.92	53.73 nM	**CYS A:195**, TYR A:51, ILE A:304, TYR A:103, TYR A:104, LEU A:124, TRP A:100, ALA A:203, TRP A:283	1
	Chlorogenic acid	-10.67	15.22 nM	**THR A:125**, MET A:128, LEU A:124, TRP A:100, LYS A:215	1
	Naringenin	-9.22	173.79 nM	**TYR A:51, TYR A:104**, TRP A:100, LEU A:124, ILE A:304, MET A:128	2
	Oleanolic acid	-11.66	2.86 nM	**ASP A:279, ARG A:182, CYS A:195**, TRP A:100, ILE A:304, TRP A:283, TYR A:51, PHE A:308, TYR A:104, LEU A:124	3
	Quercetin	-9.72	75.05 nM	**THR A:125, GLY A:121**, ARG A:182, LEU A:124, MET A:128, CYS A:195	2
	Sinapic acid	-8.62	477.55 nM	**GLY A:121, TYR A:104, ARG A:182**, TRP A:100, LEU A:124, PHE A:308, ILE A:304, TYR A:51, TYR A:103, TRP A:110, CYS A:195	3
	Syringin	-10.34	26.49 nM	**GLY A:121**, TYR A:104, TRP A:100, ARG A:182, TYR A:51	1
	Losartan	-9.21	177.30 nM	**TYR A:103, CYS A:195,** ARG A:182, TRP A:100, ILE A:304, ALA A:208, MET A:197, ILE A:196, ARG A:182	2
Beta-adrenergic receptor	Betulinic acid	+7.60	-		
	Chlorogenic acid	-13.59	109.54 pM	**PHE A:1218, ASN A:1363, GLY A:1115**, VAL A:1142, VAL A:1360, TRP A:1134,	3
	Naringenin	-11.03	8.21 nM	**ASN A:1363, CYS A:1216**, PHE A:1218, ASP A:1138, VAL A:1142, VAL A:1139	2
	Oleanolic acid	+21.79	-		
	Quercetin	-12.05	1.47 nM	**CYS A:1216, ASP A:1138, ASN A:1363**, PHE A:1218, VAL A:1139, VAL A:1142	3
	Sinapic acid	-9.06	227.89 nM	**ASP A:1138, ASN A:1363, PHE A:1218, CYS A:1216**, TRP A:1199, VAL A:1360, PHE A:1359, ASP A:1217	4
	Syringin	-13.82	74.69 pM	**ASP A:1138, ASN A:1363, GLY A:1115, TRP A:1364, ASP A:1217**, VAL A:1360, PHE A:1359, CYS A:1216, TRP A:1134, PHE A:1218	5
	Propranolol	-7.48	3.30 uM	**ASN A:1363,** PHE A:1218, ASP A:1138, PHE A:1340, PHE A:1341, VAL A:1139	**1**
Calcium channels	Betulinic acid	-6.67	12.96 uM	LYS K:435, ASP K:433	0
	Chlorogenic acid	-7.24	4.92 uM	**TYR K:437, TRP K:440**, ALA :444	2
	Naringenin	-5.59	80.52 uM	**TRP K:440, TYR K:437**, ALA K:444	2
	Oleanolic acid	-7.06	6.66 uM	**GLU K:445**, TYR K:437, TRP K:440, LEU K:434, ALA K:444	1
	Quercetin	-7.00	7.43 uM	**TRP K:440, GLU K:445**, ILE K:441, ALA K:444	2
	Sinapic acid	-5.45	101.04 uM	**TYR K:437, TRP K:440**, ILE K:441, ALA K:444	2
	Syringin	-6.26	25.74 uM	**TRP K:440, TYR K:437, ALA A:444**	3
	Amlodipine	-4.59	432.60 uM	**TYR K:437,** TRP K:440, ILE K:441, ALA K:444	1

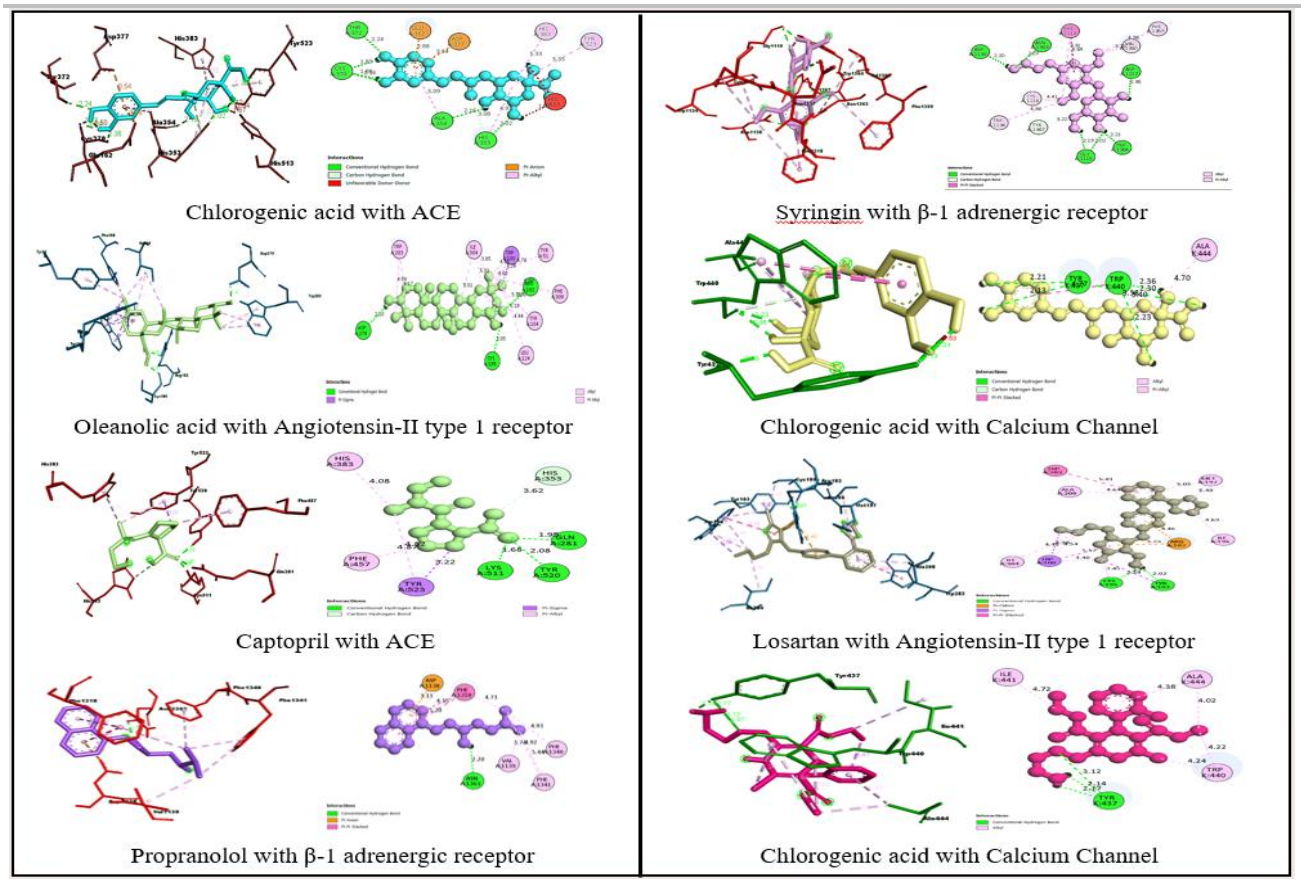


Figure 1. 3D and 2D best interactions between phytoconstituents and target proteins

3.3. Heatmap Generation: The binding affinity values of the phytochemical compounds to potential targets were tabulated in a data matrix. The analysis of this matrix was performed using the R programming (version 4.2.3), and the findings were presented in the form of a heatmap as shown in Figure 2. In this heatmap, a colour gradient between yellow and red will be used to show the range of binding energies, with blue being the most and red the least binding affinity. The heat map indicates that most phytocompounds had high and strong binding affinity with most of the targets, including ACE, Angiotensin-II receptor, β-1 adrenergic receptor, and Calcium Channel, more than the standard drugs.

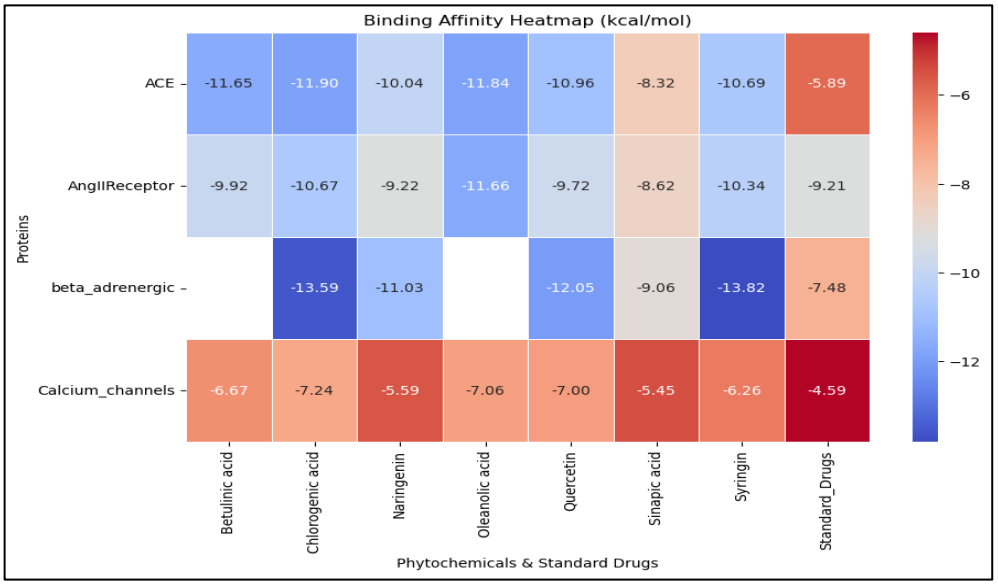


Figure 2. The binding energy between phytochemicals & targets is visualised by a heatmap

4. Discussion

Hypertension is a serious health concern in the world because of its prevalence, and it is linked to cardiovascular diseases and death [28]. The existing methods of treating hypertension are limited by side effects and resistance to therapy, which opens the chance of developing new therapeutic solutions. Hypertension has been traditionally treated with *Viscum album* [22]. This *in-silico* molecular docking experiment indicates that seven phytoconstituents of *Viscum album* can have

antihypertensive properties due to their good binding affinity with the main hypertension management proteins that include ACE, Angiotensin-II receptor, β-1 adrenergic receptor, and calcium channel. The result is that these natural compounds have the potential to provide a safer substitute to standard drugs, which usually present serious side effects.

The identification of these bioactive compounds of *Viscum album* was achieved by reviewing the literature. Then the SwissADME tool was used to calculate oral bioavailability (OB), drug-likeness (DL) and ADME properties, which enabled the selection of phytocompounds. The Protox-II web server was used in toxicity estimation. Also, hypertension-related target proteins were chosen. Molecular docking studies were done using the AutoDock4 tool in order to analyse the interaction of the selected phytochemicals with the targeted proteins. The result demonstrates that every compound had encouraging binding affinities with the targeted proteins. Amazingly, Chlorogenic acid, Oleanolic acid, Betulinic acid, Quercetin, Syringin, Naringenin, and Sinapic acid showed a high binding energy with target proteins, such as ACE, Angiotensin-II type 1 receptor, 8- adrenergic receptor, and Calcium channel. It is possible that such interactions could lead to vasodilation that is associated with the treatment effects of *Viscum album* in hypertension. Literature indicates that Chlorogenic acid has demonstrated hypotensive properties by lowering the blood pressure in spontaneously hypertensive rats due to actions either on nitric oxide synthase or on the enhancement of endothelial functions [29]. Acute intake of chlorogenic acid in humans reduced systolic and diastolic blood pressures [30]. Oleanic acid has antihypertensive effects through lipid metabolic regulation, that is, downregulation of phospholipase A2 and fatty acid synthase in spontaneously hypertensive rats [31]. Sinapic acid has been observed to have potential in the treatment of endothelial dysfunction by promoting the activity of the eNOS and Akt phosphorylation, which may be applicable in the management of hypertension [32]. The phytoconstituents, including Chlorogenic acid, Oleanolic acid and Betulinic acid, have been reported to have several pharmacological effects like antioxidant and anti-inflammatory effects [33,34]. These compounds can also act as an add-on to the general antihypertensive effect by regulating a variety of pathways that are involved in blood pressure regulation (Figure 3).

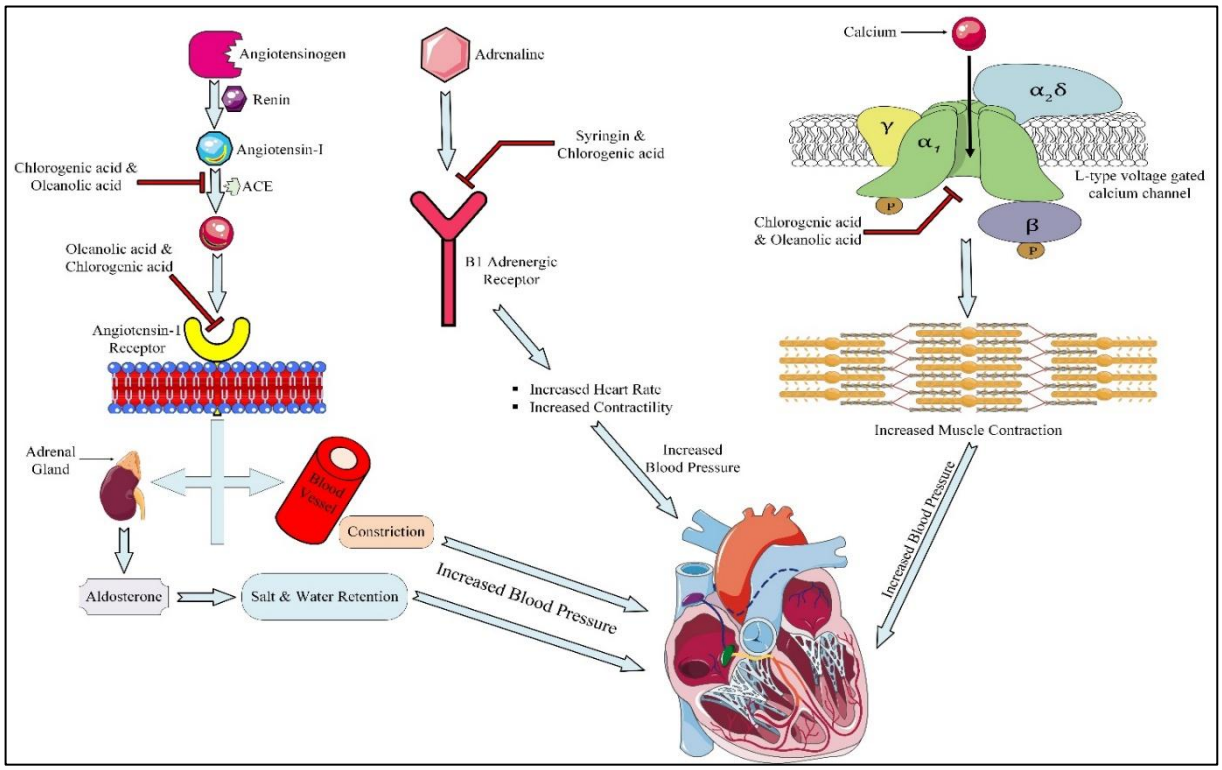


Figure 3. Mode of Action of phytoconstituents for antihypertensive activity

The target proteins investigated in this study, ACE, angiotensin II receptor, β-adrenergic receptor, and calcium channels, are not only the core of hypertension, but are also critically involved in renal pathophysiology. RAAS focuses its activities on the kidney, and the excessive production of angiotensin II by ACE will culminate in glomerular hypertension, constriction of the efferent arterioles, and the development of progressive fibrosis in the kidneys. Similarly, the stimulation of angiotensin II receptors stimulates mesangial cell proliferation, inflammatory signalling and proteinuria, all characteristic of CKD.

β-adrenergic receptors mediate renin secretion by juxtaglomerular cells, and overstimulation of these receptors leads to persistent intrarenal RAAS stimulation and sympathetic overdrive of hypertensive kidney disease. The calcium channels control renal vascular resistance and sodium reabsorption by the tubules; overload of calcium causes vasoconstriction and ischaemic damage to the tissues of the kidneys. Thus, the

process of modulating these targets is a developed nephroprotective approach that is geared towards deceleration of CKD disease and retention of the renal activity [35,36].

The present research contributes to the existing literature by shedding some light on the molecular mechanisms of action of the phytoconstituents of *Viscum album* when interacting with the key protein targets that are connected to hypertension. The high rates of interaction of these compounds with ACE, Angiotensin-II receptor, β-adrenergic receptor, and Calcium channel support their possible use as complementary hypertension therapies. These findings suggest that *Viscum album* may provide a multi-targeted hypertension treatment along with renal diseases, which might help to reduce some of the shortcomings of the single-target pharmaceutical treatments. Their therapeutic potential, as well as devising safer and more effective therapies for hypertension need further experimental and clinical confirmation.

5. Limitations

The study has limitations of an *in-silico* design. Although molecular docking can give very useful information about its possible interactions, these results should be confirmed by experimental evidence. More studies are required to evaluate the effectiveness and safety of *Viscum album* and its phytoconstituent in both *in vitro* and *in vivo*.

6. Conclusion

A sophisticated computational molecular docking analysis gives strong support for the antihypertensive properties of *Viscum album.* By demonstrating strong binding affinities of phytoconstituents with key proteins involved in hypertension and renal disease progression, such as ACE, Angiotensin-II receptor, β-adrenergic receptor, and Calcium channel, this natural compound offers a promising alternative to conventional antihypertensive drugs. The presence of bioactive compounds like Chlorogenic acid, Oleanolic acid, and Betulinic acid in *Viscum album* contributes to its therapeutic potential, as these compounds have been shown to possess antioxidant, anti-inflammatory, and cardioprotective properties. In addition to blood pressure regulation, the interactions with renal RAAS and calcium signalling targets were noted, which indicates that *Viscum album* phytoconstituents can provide nephroprotective effects in the kidney disorders linked to hypertension. The results demonstrate a need to conduct further research on *Viscum album* as a complementary therapeutic agent in the treatment of chronic kidney disease. This study underscores the therapeutic promise of *Viscum album* in hypertension and renal disease progression management, supporting their further experimental validation and clinical application. The incorporation of these natural compounds into antihypertensive therapy may serve to improve hypertension treatment outcomes because these natural compounds will give extra benefits like antioxidants and anti-inflammation, and eventually lead to safer and better control of hypertension.

7. Acknowledgement:

The authors are thankful to Dr. D. Y. Patil College of Ayurved & Research Centre, Dr. D.Y. Patil Vidyapeeth (Deemed to be University), for providing the necessary resources and support. Special thanks to the faculty and staff for their guidance and encouragement throughout this research.

8. Abbreviations

ACE: Angiotensin Converting Enzyme; **AT-1 receptor:** Angiotensin-II type 1 receptor; **RAAS:** Renin Angiotensin-Aldosterone System; **IL-6:** Interleukin 6; **DL:** Drug-likeness; **MW:** Molecular weight; **HBA:** Hydrogen bond Acceptor; **HBD:** Hydrogen bond donor; **MR:** Molar Refractivity; **NoV:** No. of Violation; **OB:** Oral Bioavailability Score; **GIA:** Gastro-intestinal Absorption; **BBB:** Blood Brain Barrier; **HT:** Hepatotoxicity; **CT:** Carcinogenicity; **MT:** Mutagenicity; **LD:** Lethal Dose; **CYP:** Cytochrome P450.

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