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Advances in Bioresearch

ORIGINAL ARTICLE

In-Silico Exploration of Phytoconstituents of *Gymnema Sylvestre* as Potential Angiotensin Receptor Inhibitors for The Treatment of Hypertension

Pravin Tajane[1*], Akash Tambe[1], Aditi Nimse[2], Abhishek Nishane[2], Prajakta Nishane[2], Akshay Pawale[2], Tejas Pawar[2]

[1*]Assistant Professor, Department of Pharmaceutical Chemistry, S.V.N.H.T's College of B. Pharmacy, Rahuri Factory, Rahuri, Ahmednagar, Maharashtra-413706, India;
[2]Research Scholar, S.V.N.H.T's College of B. Pharmacy, Rahuri Factory, Rahuri, Ahmednagar, Maharashtra-413706, India.
***Corresponding author email:** pravintajane2509@gmail.com

ABSTRACT

In both hypertensive and normotensive people, angiotensin-converting enzyme inhibitors significantly reduce mean arterial blood pressure, as well as systolic and diastolic blood pressure. Several randomized controlled trials have assessed the efficacy of angiotensin-converting enzyme inhibitors as antihypertensive agents. The exploration of plants for drug discovery is a significant area of interest and a primary contributor to contemporary medicine. Gymnema sylvestre has been documented in multiple studies as having efficacy against a range of conditions including arthritis, diuretic, anaemia, osteoporosis, hypercholesterolemia, cardiopathy, asthma, constipation, microbial infections, indigestion, and as an anti-inflammatory agent. Therefore in present study, we have investigated the major phytoconstituents of Gymnema sylvestre as potential ACE inhibitors. The selected phytoconstituents have been screened by in silico ADMET analysis followed by computational analysis. Out of docked phytoconstituents, Gymnema saponin-V, Gymnemasin-A, Gymnemic acid-I, and Stigmasterol found to be more potent than others. They inhibited the ACE significantly and can modulate its activity which can be result in lowering of blood pressure. Therefore from present investigation we concluded that, if phytoconstituents of Gymnema sylvestre isolated and treated as lead nucleus for further development of novel ACE inhibitors, we can get many potent molecules.

Keywords: *ACE; Gymnema sylvestre; hypertension, Gymnemasaponin-V; Gymnemic acid-I; ADMET; molecular docking*

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INTRODUCTION

Throughout history, herbal remedies have been utilized to address a diverse range of health ailments. However, in modern times, the primary focus pertains to the safety and effectiveness of these treatments[1]. The US Food and Drug Administration established a definition for "dietary supplement" in the Dietary Supplement Health and Education Act of 1994, which refers to an orally ingested product that contains a "dietary ingredient" with the purpose of supplementing one's diet. The constituents of a diet may encompass a variety of elements, such as vitamins, minerals, herbs, botanicals, amino acids, enzymes, organ tissues, glandulars, and metabolites. Supplements can also refer to substances that have been extracted or concentrated[2]. The ease of accessibility of dietary supplements and the common misconception that all natural products are inherently safe may lead patients to opt for these agents as a means of regulating blood pressure. The practice of self-administering dietary supplements without the guidance and supervision of a healthcare professional can pose significant risks to one's health. It is imperative for healthcare practitioners to possess knowledge regarding the various supplements that are utilized to promote a healthy cardiovascular system[3–5].

In both hypertensive and normotensive people, angiotensin-converting enzyme inhibitors significantly reduce mean arterial blood pressure, as well as systolic and diastolic blood pressure. Several randomized controlled trials have assessed the efficacy of angiotensin-converting enzyme inhibitors as antihypertensive agents[6–8]. The exploration of plants for drug discovery is a significant area of interest and a primary contributor to contemporary medicine. Only 5–15% of plants have been studied for their potential as medicines, however around 25% of contemporary medications have a plant origin. *Gymnema sylvestre* is a member of the *Apocynaceae* family and has been historically utilized for the management of diverse medical conditions. This botanical specimen is a naturally occurring herbaceous plant that can be found growing in the wild within the geographical regions of India, Africa, Australia, and China. This particular botanical specimen is commonly referred to as 'Gurmur' and is acknowledged for its hypoglycemic effects[9–12]. The Ayurvedic system of medicine has recognized *Gymnema sylvestre* as a significant botanical for treating diabetes. Additionally, this plant has been included in the Indian Pharmacopoeia as an anti-diabetic agent. The plant in question has been found to be efficacious against a variety of serious illnesses, including but not limited to cardiovascular diseases, asthma, cancer, diabetes, and obesity. As a result, it has been incorporated into a range of preparations, including tea bags, health tablets, and food supplements. *Gymnema sylvestre* has been documented in multiple studies as having efficacy against a range of conditions including arthritis, diuretic, anaemia, osteoporosis, hypercholesterolemia, cardiopathy, asthma, constipation, microbial infections, indigestion, and as an anti-inflammatory agent[13–15].Therefore in present study, we have investigated the major phytoconstituents of *Gymnema sylvestre* as potential ACE inhibitors. The selected phytoconstituents have been screened by in silico ADMET analysis followed by computational analysis.

MATERIAL AND METHODS

Pharmacokinetics Predictions of Phytoconstituents

Utilizing molinspiration and SwissADME servers, Lipinski rule of five and pharmacokinetic features of phytoconstituents were investigated[16,17]. An *in silico* toxicity prediction of phytoconstituents has been made using ProTox-II, a webserver that is freely available(http://tox.charite.de/protox_II)[18].

Molecular Docking Studies

In order to further optimization, the phytoconstituents were subjected for binding affinity studies with human angiotensin receptor. The Autodock vina 1.1.2 with PyRx Virtual Screening Tool 0.8 software of the Chimera version 1.10.2[19] and the Biovia Discovery studio was used to perform molecular docking[20]. The structures of phytoconstituents and native ligand were drawn using ChemDraw Ultra 8.0 version and saved in mol file format. The energy minimization was executed by Universal Force Field (UFF) in PyRx software[21]. The crystal structure of the XFEL structure of human angiotensin receptor (PDB ID: 4YAY) was obtained from the RCSB Protein Data Bank (https://www.rcsb.org/). The 3D ribbon view of angiotensin receptor with native ligand is illustrated in Fig. 1. The binding mode and binding affinity of native ligand was used to validate the results of phytoconstituents. With an exhaustiveness value of 8, the three-dimensional grid box (size_x = 49.1531A^{o}, size_y = 38.5281A^{o}, size_z = 42.6578A^{o}) was modified for molecular docking simulations. The complete molecular docking approach was carried out in accordance with the methods outlined by S. L. Khan *et al.*[22–27].

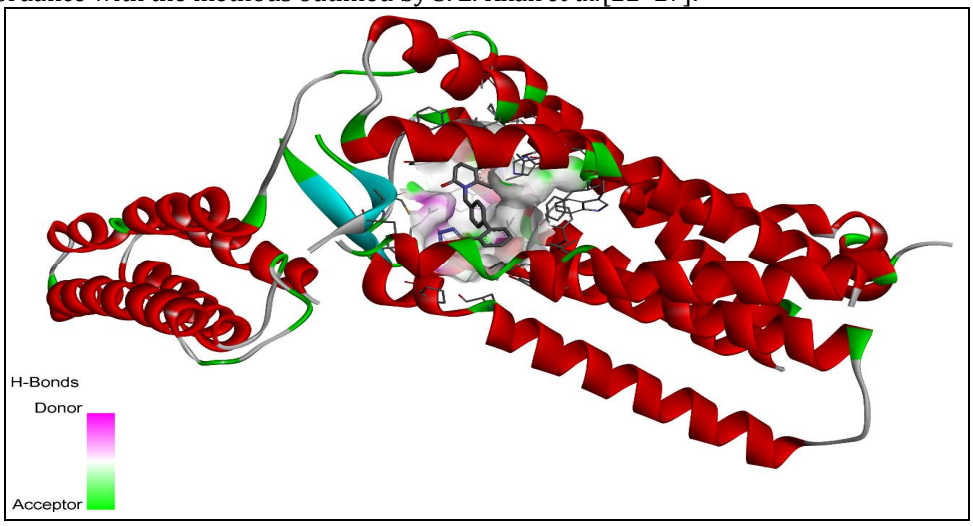


Fig. 1. The 3D ribbon view of angiotensin receptor with native ligand

RESULTS AND DISCUSSION

Pharmacokinetics Predictions of Phytoconstituents

In present study we have investigated some natural phytoconstituents as potential human angiotensin receptor inhibitors [28]. The physicochemical properties of designed molecules Native ligands, Gymnemanol, Gymnemasaponin_V, Gymnemasin_A, Gymnemic acid_I_, Gymnemoside_A, Gymnestrogenin, Lupeol, Quercitol, Stigmasterol are tabulated in Table 1. In physicochemical analysis, values of all the molecules were calculated i.e. molecular weights, nHA, nHD, nRot, Van der Waals volume, and TPSA. In present investigation most of these parameters were within the acceptable range and displayed optimum oral bioavailability which indicates they can be developed to be delivered through oral route [29,30], but few molecules disobeyed Lipinski rule due to its high molecular weight, but still it can be a potential enzyme inhibitor.

The drug-likeness properties of molecules are exemplified in Table 2. The different parameters such as QED, NPscore, Lipinski rule, Pfizer rule, GSK rule, Golden Triangle, and Chelator rule were calculated. Typically, the natural product-likeness score, also known as the NPscore, falls somewhere in the range of -0.7 to 1. If the score is higher, then there is a greater likelihood that the molecule in question is an NP[31,32]. All the phytoconstituents displayed NP-like properties within the range. The compounds satisfying the GSK rule may have a more favorable ADMET profile but unfortunately, only Quercitol accepted the rule. The compound Gymnemanol accepted the Golden Triangle rule may have a more favorable ADMET profile.

The absorption parameters of the molecules are illustrated in Table 3. As a model of how medications are absorbed by the human digestive tract, the human colon epithelial cancer cell line known as Caco-2 is employed. Caco-2 permeability is optimum when the value is higher than -5.15 Log unit and fortunately all the molecules displayed optimum Caco-2 permeability[33]. Many of the molecules displayed Pgp-inhibitor and Pgp-substrate activity. All the phytoconstituents displayed excellent human intestinal absorption (HIA). F20% and F30% bioavailability of all the molecules were within the range of acceptable values.

The distribution and metabolism profile of molecules are depicted in Table 4. Plasma protein binding (PPB, <90%), drugs with high protein-bound may have a low therapeutic index; many of the molecules displayed PPB less than 90%. Volume distribution (VD, optimal 0.04-20L/kg) of all the molecules were within the range of acceptable limit. None of the molecule displayed BBB penetration potential. Cytochrome enzymes play an important role in drug metabolism therefore being its substrate or inhibitor contributes to the drug action. In present investigation, these molecules showed all the Cytochrome enzymes inhibition.[34].

An excretion and toxicity profile of molecules are tabulated in Table 5. All of the molecules displayed high clearance rate (CL, High: >15 mL/min/kg; moderate: 5-15 mL/min/kg; low: <5 mL/min/kg). All the molecules exhibited short half-life ($T_{1/2}$, <3h). Toxicity profile of the molecules suggested favorable properties and displayed many of the values were within the range. None of the molecules showed Human Hepatotoxicity. Drug Induced Liver Injury was seen. Maximum Recommended Daily Dose, AMES Toxicity, Rat Oral Acute Toxicity was shown with all the polymers. None of the molecules showed Carcinogenicity and Respiratory Toxicity. An environmental toxicity profile (Bio concentration factors, IGC_{50}, $LC_{50}FM$, and $LC_{50}DM$) of designed molecules are demonstrated in Table 6. An environmental toxicity profile of the molecules were optimum and within the acceptable range.

Table 1. Lipinski rule of 5 and Veber's rule calculated for molecules

Compound name	Physicochemical Property							
	Molecular Weight	Volume	nHA	nHD	nRot	TPSA	logS	logP
NL	438.22	458.603	7	1	6	87.66	-5.961	3.695
Gymnemanol	490.37	525.968	5	5	2	101.15	-3.914	3.614
Gymnemasaponin_V	1122.58	1073.861	24	16	14	397.52	-2.741	0.402
Gymnemasin_A	910.49	900.461	17	10	11	282.59	-3.558	1.976
Gymnemic acid_I_	820.46	828.122	14	7	10	229.74	-4.008	2.903
Gymnemoside_A	806.45	810.826	14	7	10	229.74	-4.017	2.76
Gymnestrogenin	518.4	560.56	5	5	2	101.15	-3.817	3.319
Lupeol	426.39	490.807	1	1	1	20.23	-6.643	6.753
Quercitol	164.07	147.727	5	5	0	101.15	-0.08	-2.116
Stigmasterol_	412.37	479.432	1	1	5	20.23	-7.059	6.909

Table 2: Drug-likeness properties of designed derivatives

Compound name	Medicinal Chemistry						
	QED	NPscore	Lipinski Rule	Pfizer Rule	GSK Rule	Golden Triangle	Chelator Rule
NL	0.478	-1.033	Accepted	Accepted	Rejected	Accepted	0
Gymnemanol	0.376	3.008	Accepted	Accepted	Rejected	Accepted	0
Gymnemasaponin_V	0.075	1.797	Rejected	Accepted	Rejected	Rejected	0
Gymnemasin_A	0.064	2.776	Rejected	Accepted	Rejected	Rejected	0
Gymnemic acid_I_	0.081	2.918	Rejected	Accepted	Rejected	Rejected	0
Gymnemoside_A	0.081	3.13	Rejected	Accepted	Rejected	Rejected	0
Gymnestrogenin	0.337	2.603	Accepted	Accepted	Rejected	Rejected	0
Lupeol	0.421	3.054	Accepted	Rejected	Rejected	Rejected	0
Quercitol	0.266	1.517	Accepted	Accepted	Accepted	Rejected	0
Stigmasterol_	0.457	2.802	Accepted	Rejected	Rejected	Rejected	0

Table 3: An absorption parameters of developed molecules

Compound name	Absorption						
	Caco-2 Permeability	MDCK Permeability	Pgp-inhibitor	Pgp-substrate	HIA	F20%	F30%
NL	-5.074	2.4e-05	0.997	0.989	0.04	0.003	0.364
Gymnemanol	-5.09	1.4e-05	0.011	0.009	0.009	0.929	0.121
Gymnemasaponin_V	-6.406	0.000102	0.000102	0.058	0.999	0.999	1.0
Gymnemasin_A	-5.953	7.3e-05	0.984	0.063	0.919	0.361	0.975
Gymnemic acid_I_	-5.549	6.2e-05	0.959	0.074	0.783	0.109	0.841
Gymnemoside_A	-5.571	6.6e-05	0.921	0.06	0.828	0.567	0.907
Gymnestrogenin	-5.272	9e-06	0.079	0.005	0.014	0.956	0.889
Lupeol	-5.095	1.3e-05	0.031	0.0	0.003	0.731	0.877
Quercitol	-5.264	0.00052	0.002	0.652	0.807	0.012	0.969
Stigmasterol_	-4.623	1.5e-05	0.287	0.019	0.021	0.953	0.599

Table 4: Distribution and metabolism profile of developed molecules

Compound name	Distribution				Metabolism									
					CYP1A2		CYP2C19		CYP2C9		CYP2D6		CYP3A4	
	PPB(%)	VD	BBB Penetration	Fu	Inhibitor	substrate	Inhibitor	substrate	Inhibitor	substrate	Inhibitor	substrate	Inhibitor	substrate
NL	97.36	0.765	0.198	1.299	0.79	0.251	0.949	0.058	0.939	0.868	0.628	0.072	0.924	0.629
Gymnemanol	87.50	0.735	0.484	11.53	0.009	0.112	0.005	0.797	0.062	0.053	0.003	0.093	0.728	0.232
Gymnemasaponin_V	55.38	-0.382	0.1	17.90	0.0	0.083	0.0	0.062	0.0	0.001	0.0	0.033	0.04	0.002
Gymnemasin_A	79.55	0.428	0.127	7.201	0.001	0.062	0.001	0.24	0.002	0.017	0.003	0.056	0.103	0.025
Gymnemic acid_I_	83.30	0.39	0.066	5.640	0.003	0.09	0.002	0.426	0.012	0.027	0.006	0.061	0.122	0.06
Gymnemoside_A	86.03	0.406	0.077	6.266	0.0002	0.071	0.002	0.371	0.016	0.036	0.012	0.077	0.159	0.08
Gymnestrogenin	85.46	0.776	0.535	12.47	0.002	0.228	0.011	0.901	0.067	0.04	0.003	0.026	0.893	0.694
Lupeol	98.46	1.454	0.34	1.791	0.039	0.597	0.079	0.954	0.099	0.615	0.071	0.902	0.249	0.452
Quercitol	11.03	0.506	0.377	76.02	0.039	0.044	0.012	0.125	0.001	0.654	0.003	0.117	0.004	0.014
Stigmasterol_	91.45	2.183	0.516	1.038	0.056	0.662	0.111	0.95	0.145	0.2	0.078	0.849	0.5	0.835

Table 5: Excretion and toxicity profile of developed molecules

Compound name	Excretion		Toxicity									
	CL	T1/2	H-HT	DILI	AMES Toxicity	Rat Oral Acute Toxicity	FDAMDD	Skin Sensitization	Carcinogenicity	Eye Corrosion	Eye Irritation	Respiratory Toxicity
NL	1.063	0.042	0.811	0.88	0.983	0.257	0.891	0.804	0.064	0.016	0.003	0.008
Gymnemanol	4.875	0.609	0.064	0.012	0.004	0.958	0.994	0.323	0.27	0.021	0.019	0.991
Gymnemasaponin_V	-0.099	0.84	0.126	0.004	0.061	0.097	0.544	0.316	0.029	0.003	0.007	0.369
Gymnemasin_A	0.726	0.765	0.245	0.084	0.037	0.051	0.981	0.203	0.093	0.003	0.007	0.912
Gymnemic acid_I_	1.067	0.712	0.274	0.34	0.018	0.143	0.944	0.169	0.025	0.003	0.008	0.751
Gymnemoside_A	1.187	0.678	0.387	0.23	0.029	0.108	0.934	0.047	0.033	0.003	0.008	0.573
Gymnestrogenin	3.841	0.244	0.625	0.009	0.009	0.888	0.986	0.325	0.773	0.006	0.016	0.988
Lupeol	4.871	0.049	0.091	0.081	0.001	0.206	0.926	0.608	0.005	0.932	0.593	0.621
Quercitol	1.531	0.679	0.034	0.044	0.065	0.014	0.004	0.135	0.018	0.012	0.805	0.064
Stigmasterol_	4.851	0.023	0.145	0.124	0.01	0.454	0.961	0.266	0.032	0.003	0.015	0.415

Table 6: Environmental toxicity profile of designed molecules

Compound name	Environmental toxicity			
	Bioconcentration Factors	IGC50	LC50FM	LC50DM
NL	2.281	4.423	3.403	5.095
Gymnemanol	0.718	4.492	5.919	6.621
Gymnemasaponin_V	1.276	4.693	5.377	6.01
Gymnemasin_A	0.701	4.518	5.695	6.04
Gymnemic acid_I_	0.934	5.091	6.608	6.727
Gymnemoside_A	0.755	4.762	6.11	6.521
Gymnestrogenin	0.737	3.844	4.648	5.451
Lupeol	2.804	5.746	7.098	6.983
Quercitol	0.226	0.89	1.1	2.769
Stigmasterol_	3.147	5.142	6.572	6.704

Molecular Docking Studies

The molecular interactions of the titled compounds are exemplified in Table 7. Table 8 depicts the most potent compounds' 2D-and 3D-docking orientations. The binding affinities of phytoconstituents with the enzymes with crystal structure **4yay** are discussed in the below section.

Native Ligand exhibited -11 kcal/mol of binding affinity and formed two conventional hydrogen bonds with Ala21 and Trp84. It also formed electrostatic and hydrophobic interactions (Pi-Anion, Pi-pi stacked, and Pi-alkyl) with Asp, Tyr92, Trp84, Val108, and Ile288. Gymnemanol showed docking score of -9.3 kcal/mol and formed four conventional hydrogen bonds with Cys180 and Arg167. Gymnemasaponin_V exhibited -10.8 binding affinity and formed hydrogen bonds (Conventional hydrogen bond and carbon hydrogen bond) with Cys18, Asp281, Asp263, Phe182, Arg167, Gln267, His256, Ser105 and Ala181. Gymnemasin_A exhibited -10.4 kcal/mol of binding affinity and formed three conventional hydrogen bonds and two carbon hydrogen bonds with Asp263, Cys18, Lys20, Ser15, Val108, Ile288, Phe77 and Tyr292. Gymnemic acid_I showed -10 kcal/mol of binding affinity and formed five hydrogen bonds (conventional hydrogen bond and carbon hydrogen bond) with Leu13, Cys18, Lys20, Arg167, and Ser15. It also formed hydrophobic Interactions (Pi-sigma) with Trp84.

Gymnemoside_A exhibited -8.9 kcal/mol of binding affinity and formed eight conventional hydrogen bonds with Cys18, Asp281, His256, Lys20, Ala21, and Tyr92. It also formed hydrophobic Interactions (Pi-Sigma) with Tyr92. Gymnestrogenin showed -9.6 kcal/mol of binding affinity and formed three hydrogen bonds (Conventional and carbon hydrogen bonds) with Cys18 and Pro19. It also formed hydrophobic Interactions with Tyr92. Lupeol_259846 exhibited -9.8 kcal/mol of binding affinity and formed one conventional hydrogen bond with Gln267. Quercitol exhibited docking score of -4.7 kcal/mol and formed one conventional hydrogen bond with Arg167. It also formed hydrophobic Interactions (Pi-pi stacked, Pi-alkyl) Trp84, Val108, Ile288. Stigmasterol showed -10.3 kcal/mol of binding affinity and formed hydrophobic Interactions (Pi-sigma, Alkyl, Pi-alkyl) with Tyr92, Trp84, Val179, Val108, Ile288, Met284, Pro285, Tyr35, Trp84 and Tyr92. Out of docked phytoconstituents, Gymnemasaponin-V, Gymnemasin-A,

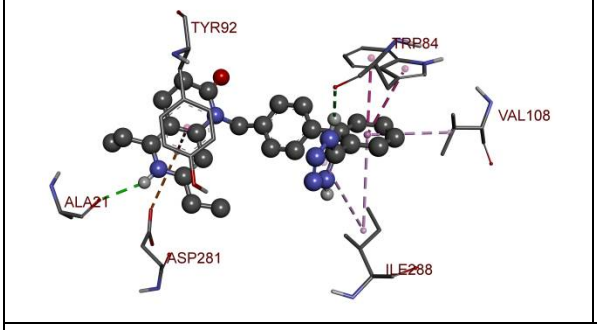
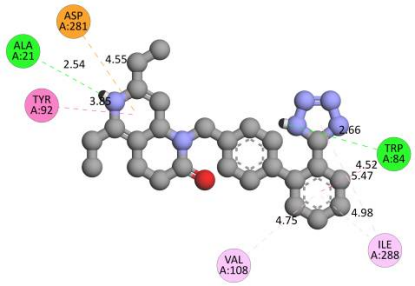
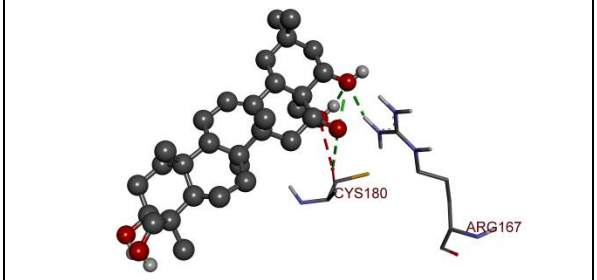
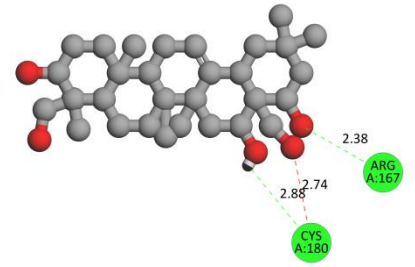
Gymnemic acid-I, and Stigmasterol found to be more potent than others. They inhibited the ACE significantly and can modulate its activity which can be result in lowering of blood pressure.

Table 7. The active amino residues, bond length, bond category, bond type, ligand energies, and docking scores

Active amino acids	Bond length	Bond Type	Bond category	Ligands energy	Docking score
NL					
ALA21	2.54263	Hydrogen Bond	Conventional Hydrogen Bond	692.35	-11
TRP84	2.66233				
ASP281	4.55309	Electrostatic	Pi-Anion		
TYR92	3.85004	Hydrophobic	Pi-Pi Stacked		
TRP84	3.90583				
TRP84	4.0323				
VAL108	4.74971		Pi-Alkyl		
ILE288	4.97557				
ILE288	5.473				
Gymnemanol					
CYS180	2.40311	Hydrogen Bond	Conventional Hydrogen Bond	965.18	-9.3
	2.88409				
	1.8603				
ARG167	2.37925				
Gymnemasaponin-V					
CYS18	2.15088	Hydrogen Bond	Conventional Hydrogen Bond	821.81	-10.8
ASP281	2.4214				
ASP263	2.62656				
ASP263	2.62962				
PHE182	2.32531				
	2.35018				
ASP263	1.98957				
ARG167	2.95648				
GLN267	2.16173				
HIS256	3.6103		Carbon Hydrogen Bond		
SER105	3.67666				
ALA181	3.43372				
Gymnemasin-A					
ASP263	2.27182	Hydrogen Bond	Conventional Hydrogen Bond	847.37	-10.4
CYS18	2.28703				
LYS20	2.0451				
SER15	3.55133		Carbon Hydrogen Bond		
SER15	3.5314				
VAL108	4.28831	Hydrophobic	Alkyl		
ILE288	4.23766				
PHE77	4.87218		Pi-Alkyl		
TYR292	4.13672				
Gymnemic acid-I					
LEU13	1.92618	Hydrogen Bond	Conventional Hydrogen Bond	962.63	-10
CYS18	2.45668				
LYS20	2.25491				
ARG167	2.06373				

SER15	3.62691		Carbon Hydrogen Bond		
TRP84	3.43808	Hydrophobic	Pi-Sigma		
TRP84	3.88294				
Gymnemoside-A					
CYS18	2.92169	Hydrogen Bond	Conventional Hydrogen Bond	652.76	-8.9
ASP281	2.56643				
HIS256	2.27556				
	2.16909				
	2.256				
LYS20	2.87176				
ALA21	1.99755				
TYR92	2.19452				
TYR92	3.93015	Hydrophobic	Pi-Sigma		
Gymnestrogenin					
CYS18	2.77592	Hydrogen Bond	Conventional Hydrogen Bond	475.48	-9.6
	2.0663				
PRO19	3.28003		Carbon Hydrogen Bond		
TYR92	3.98625	Hydrophobic	Pi-Sigma		
Lupeol					
GLN267	2.42829	Hydrogen Bond	Conventional Hydrogen Bond	596.76	-9.8
Quercitol					
ARG167	2.68486	Hydrogen Bond	Conventional Hydrogen Bond	485.28	-4.7
TRP84	3.78181	Hydrophobic	Pi-Pi Stacked		
TRP84	4.43668				
VAL108	5.25373		Pi-Alkyl		
ILE288	5.31882				
Stigmasterol					
TYR92	3.89997	Hydrophobic	Pi-Sigma	341.86	-10.3
TRP84	3.73913				
TRP84	3.8889				
VAL179	5.10522		Alkyl		
VAL108	4.51668				
ILE288	5.00882				
MET284	5.29284				
PRO285	4.79326				
TYR35	5.00438		Pi-Alkyl		
TRP84	5.07067				
TRP84	5.24298				
TYR92	5.12851				
TYR92	4.63151				

Table 8. The 3D- and 2D-docking poses of the molecules

3D-docking poses	2D-docking poses
NL	
	
Gymnemanol	
	
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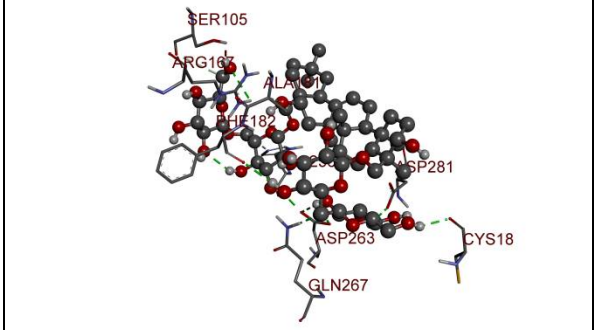	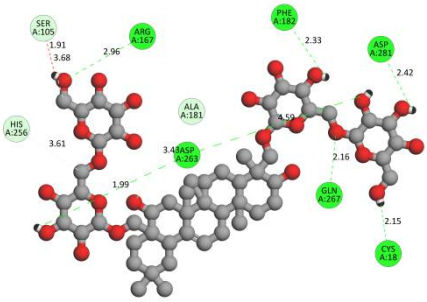
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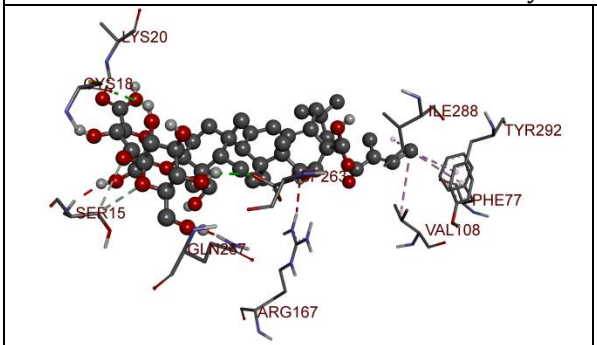
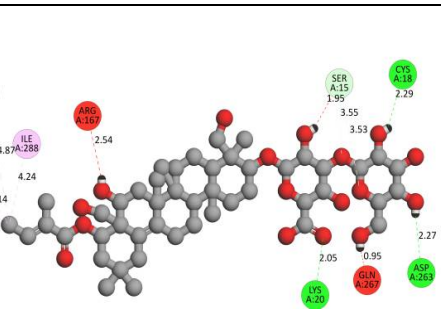
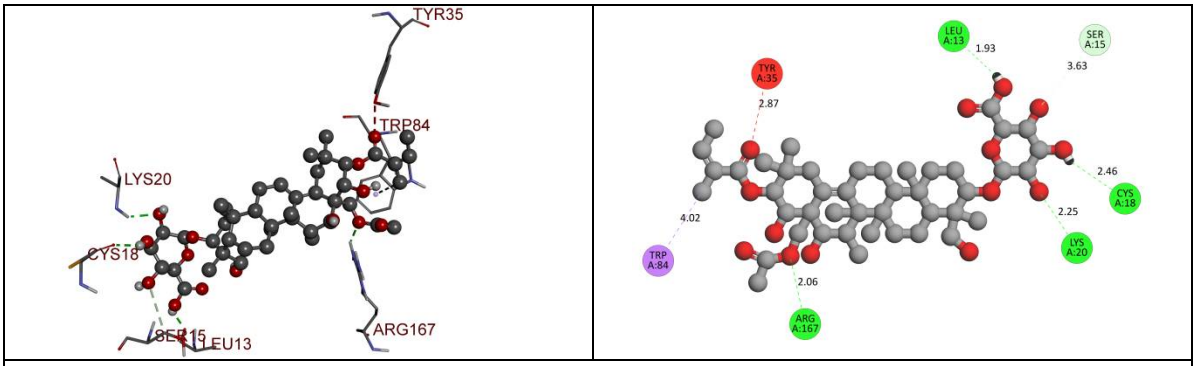
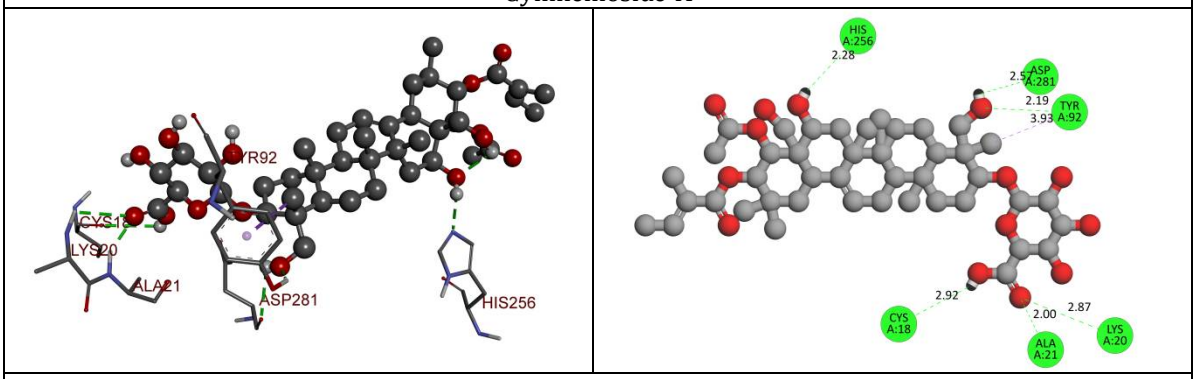
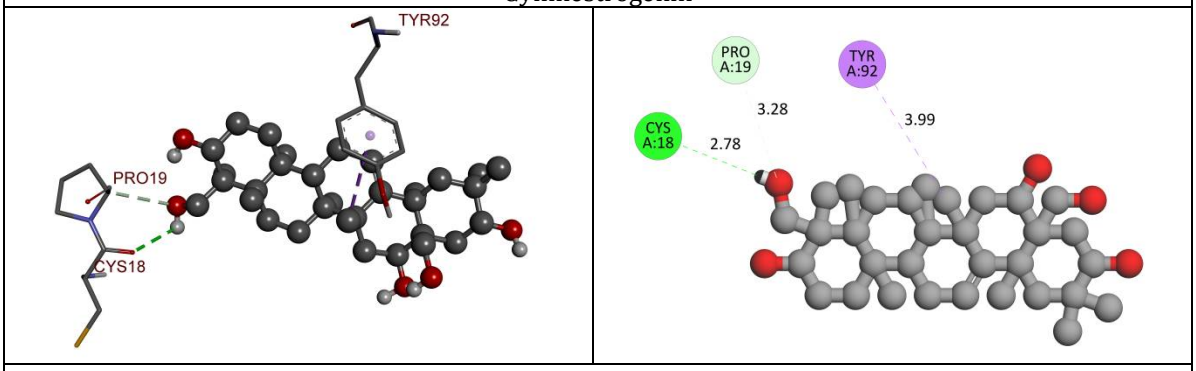
	
Gymnemic acid-I	



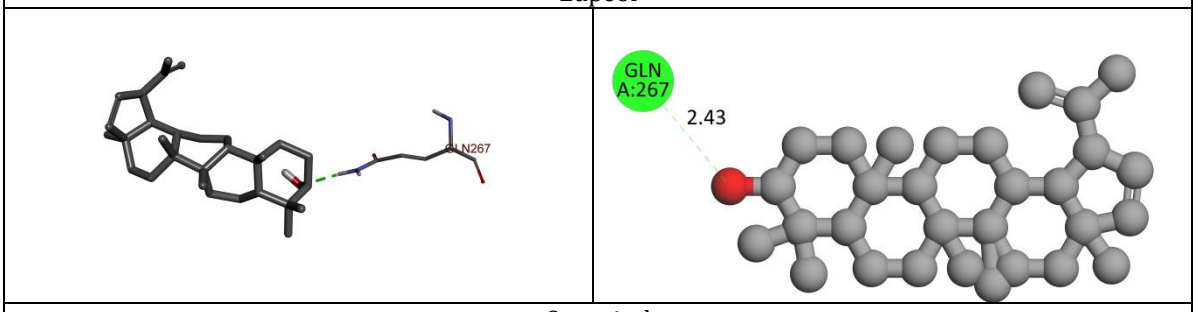
Gymnemoside-A



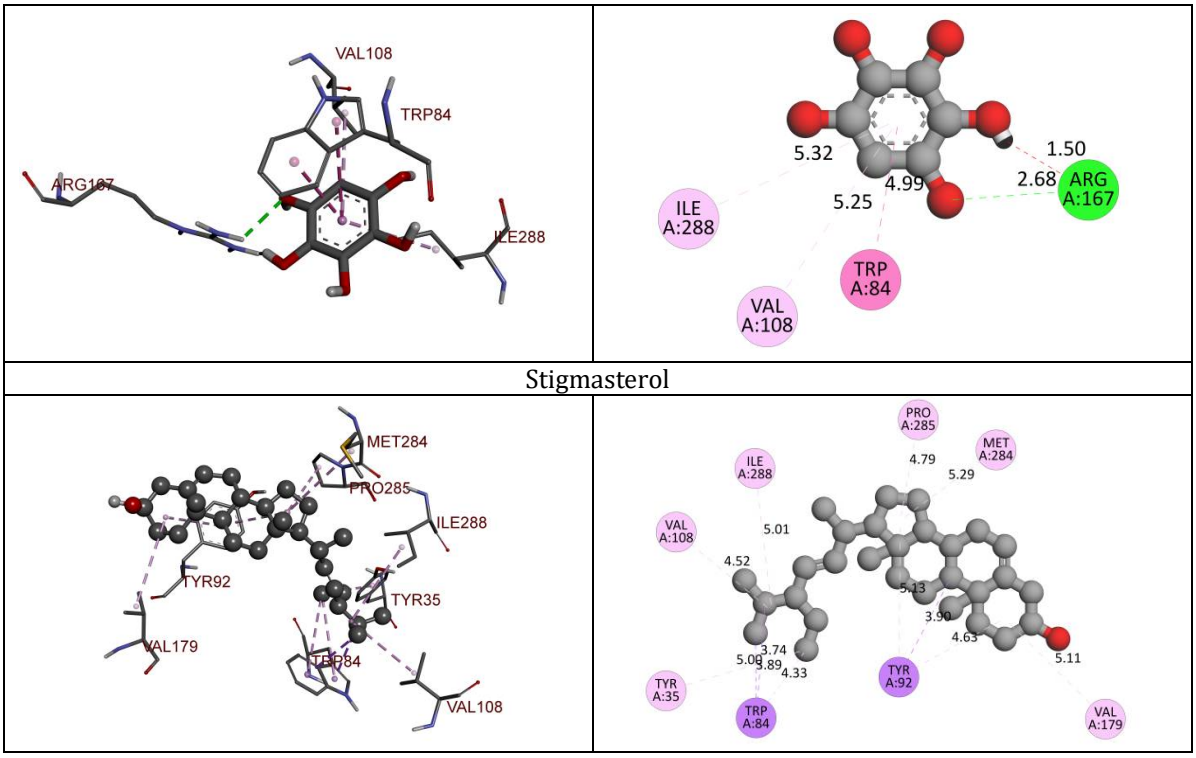
Gymnestrogenin



Lupeol



Quercitol



CONCLUSION

Angiotensin-converting enzyme inhibitors have been observed to significantly decrease mean arterial blood pressure, systolic blood pressure, and diastolic blood pressure in individuals with both hypertension and normotension. Numerous randomised controlled trials have evaluated the effectiveness of angiotensin-converting enzyme inhibitors in treating hypertension. The investigation of botanical specimens for the purpose of identifying potential therapeutic agents is a crucial field of inquiry and a key driver of modern healthcare. Numerous studies have documented the efficacy of *Gymnema sylvestre* in treating a variety of conditions, such as arthritis, diuretic, anaemia, osteoporosis, hypercholesterolemia, cardiopathy, asthma, constipation, microbial infections, indigestion, and as an anti-inflammatory agent. The current study aims to explore the primary phytoconstituents found in *Gymnema sylvestre* and their potential as inhibitors of angiotensin-converting enzyme (ACE). The phytoconstituents that were chosen underwent in silico ADMET analysis and subsequent computational analysis. Among the phytoconstituents that were docked, Gymnema saponin-V, Gymnemasin-A, Gymnemic acid-I, and Stigmasterol were identified as exhibiting greater potency compared to the remaining compounds. The ACE was significantly inhibited by the compound under investigation, potentially leading to a modulation of its activity and subsequent reduction in blood pressure. Thus, based on the findings of our study, it can be inferred that utilizing the phytoconstituents of *Gymnema sylvestre* as a lead nucleus for the development of novel ACE inhibitors has the potential to yield numerous potent molecules.

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