Available online on 15.09.2025 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

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Research Article

Exploring the beneficial effect and therapeutic mechanism of phytochemicals present in *Selenicereus undatus* against Hypertension based on Molecular docking studies

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Article Info:

Article History:

Received 17 June 2025
Reviewed 26 July 2025
Accepted 16 August 2025
Published 15 Sep 2025

Cite this article as:

Habiba U, Bhowmick P, Khatun R, Seal R, Ghosh I, Karmakar A, Mandal D, Exploring the beneficial effect and therapeutic mechanism of phytochemicals present in *Selenicereus undatus* against Hypertension based on Molecular docking studies, Journal of Drug Delivery and Therapeutics. 2025; 15(9):27-39
DOI:
http://dx.doi.org/10.22270/jddt.v15i9.7348

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Abstract

Aim: Hypertension is a common disease caused by high blood pressure increasing risks of heart and kidney problems. It involves overactivity of angiotensin converting enzyme which primarily raises blood pressure by narrowing blood vessels. *Selenicereus undatus* exhibits promising therapeutic potential against hypertension, attributed to its rich phytochemical profile including flavonoids, carotenoids, betalains and polyphenols. These compounds demonstrate antioxidative and Anti-inflammatory properties which mitigate oxidative stress — a key contributor to endothelial dysfunction and elevated blood pressure. Many studies reveal that *Selenicereus undatus* has the ability to improve lipid metabolism by reducing LDL cholesterol and triglycerides while enhancing HDL levels, indirectly supporting cardiovascular health.

Materials and Methods: In this study 3 targets i.e. ACE receptor, AT1 receptor and Beta-Adrenergic receptor were selected on the basis of their mechanism of action in hypertension. The docking analysis was carried out by utilising PyRx 0.8 virtual screening and the visualization of protein-ligand interaction was investigated by utilising the BIOVIA Discovery Studio Visualizer.

Results: Docking simulation of active compounds from *Selenicereus undatus* against the ACE receptor shows that Beta-carotene (-11.0 kcal / mole), Betanin (-10.2 kcal / mole) and Quercetin (-8.3 kcal / mole) have the highest binding affinity. In the characteristic binding to the AT1 receptor, Beta carotene (-9.2 kcal / mole), Betanin (-8.5 kcal / mole) and Tocopherol (-8.1 kcal / mole) showed highest binding affinity. Docking analysis of Beta-Adrenergic receptor showed impressive binding affinities of Beta-carotene (-9.0kcal / mole).

Conclusion: On the basis of binding affinity and pharmacokinetic parameters our findings strongly support the potential use of phytoconstituents from *Selenicereus undatus* as a medicinal herb that might be taken in daily life to reduce high blood pressure. Further, additional research, i.e. in vitro and in vivo trials on the same constituents, is required to confirm our results and the clear picture of the mechanism of action by which the medicinal plant demonstrated their antihyperlipidemic effects.

Keywords: Hypertension, *Selenicereus undatus*, Phytoconstituents, Molecular docking, ADMET, Drug likeness.

1. INTRODUCTION:

The term 'cardiovascular disorder'(CVD) is a group of illnesses that impact the heart or blood vessels, including the veins and arteries. An increase in arterial pressure is the characteristic of hypertension, also known as high blood pressure. It is a chronic medical illness. The force of circulating blood on the blood artery wall is known as blood pressure. Cardiac output and peripheral vascular resistance determine it. Baroreceptor reflexes control blood pressure by acting through the autonomic nervous system. The blood pressure follows as- Systolic blood pressure, Diastolic blood pressure, Pulse pressure [1]. The hypertension is a chronic medical condition that is characterized by having a diastolic blood pressure of 80mmHg or higher and systolic blood pressure is of 120mmHg.The hypertension is classified as 2 types, as- Essential or primary hypertension, Secondary hypertension. High blood pressure has damaging effects on the heart, brain, kidneys, and eyes. Hypertension is also renowned as the "Silent Killer". Hypertension develops through a number of processes. The renin angiotensin aldosterone system (RAAS) is a hormone system that regulates blood pressure and fluid balance in the human body. It causes vasoconstriction of arterioles, increase sodium retention, water reabsorption and increase blood volume [2]. Thus, it causes high blood pressure. Mineralocorticoid and glucocorticoid play a role in increasing blood pressure. In this world wide, hypertension is a leading cause of premature deaths. Hypertension is one of the biggest burdens in the world. In India, hypertension has become a prominent risk

factor. It is predicted that the burden of hypertension in India will almost double from 118 million in 2000 to 215 million by 2030. Hypertension is directly responsible for 56% of all stroke deaths and 25% of all coronary heart disease deaths in India. A previous systemic review reported that the prevalence rates of hypertension in urban and rural areas of India ranged from 13.9% to 46.3% and 4.5% to 58.8% [3,4]. According to NFHS-5(2019-2021), the prevalence of hypertension among women in rural India is 20.2% and men, it is 22.7% [5]. Obesity, Unhealthy Diet, Physical Inactivity, consuming huge amounts of alcohol, Stress, Tobacco use, high cholesterol are of great significance and principle cause of hypertension. Treatment of hypertension divided into two categories i.e. Weight loss, less Sodium Consumption, Physical activities, Smoking Cessation, Stress Reduction, Healthy diet etc [6] and the medication includes consumption of synthetic hypertension drugs. Apart from their ability to reduce high blood pressure, these synthetic compounds have other positive effects as well. However, administering them for long period of time could end up with unfavourable side effects.

Selenicereus undatus is commonly referred to as Pitaya and belongs to the *Cactaceae* family and genus is *Hylocereus* [7]. Number of *Hylocereus spp.* is 22n, so it is diploid in nature [8]. It is abunded with phytoconstituents viz. Gallic acid, Vanillic acid, Syringic acid, Caffeic acid, p-Coumaric acid, Quercetin, Catechin, Beta-carotene, Betanin, Tocopherols. Additionally, there are numerous therapeutic activities such as Antioxidant activity, Anti-inflammatory activity, Anticancer activity, Anti-diabetic activity, Antiviral activity, Cardioprotective effect [9] and many more properties have been reported from this plant but there is no scientific evidence available for antihypertension activity using *Selenicereus undatus* [10].

Molecular docking is a computer-aided approach which serves to identify specific molecules in accordance with their free binding energy and demonstrates structural hypotheses concerning the assessment of protein ligand interactions which plays a key role in determining molecular targets or receptors for various ligands. This approach has benefits in terms of decreasing errors in laboratory research, leads to lower costs and faster responses.

2. METHODOLOGY:

2.1 Software and Tools:

Protein Data Bank (PDB), PubChem, PyRx, Molegro Molecular Viewer, Discovery Studio Visualizer.

2.2 Ligand Structure Preparation:

The phytoconstituents viz. Gallic acid, Vanillic acid, Syringic acid, Caffeic acid, p-Coumaric acid, Quercetin, Catechin, Beta-carotene, Betanin, Tocopherols have been diagnosed from the chosen medicinal plant *Selenicereus undatus* and the 2D structures of the ligands were obtained from PubChem chemical libraries and saved as SDF format.

2.3 Target Prediction:

In order to identify the various possible targets based on the fit score, the Swiss Target Prediction tool was implemented. The canonical SMILES of chemical compounds have been presented on the website. The species was selected as homo sapiens, and all additional parameters have been retained as the default.

2.4 Protein Structure Preparation:

The 3D structures of targeted receptor proteins related to metabolism of lipids were recognized by Target Prediction and obtained from the Protein data bank (PDB). The three-dimensional (3D) coordinates of the crystal structure of Angiotensin receptor inhibitor in complex with Notum_Valsartam, PDB id-7BM1(with a Resolution: 1.37 Å), Angiotensin-Converting Enzyme Inhibitors in complex with Lisinopril, PDB id-1O86(with a Resolution: 2.0 Å), Beta-Adrenergic blocker in complex with Metoprolol, PDB id-6PS5(with a Resolution:2.90Å). In order to perform docking analysis, the target was initially determined and afterwards 3D structure of the above receptors were obtained. It is commonly accepted that the PDB file format is unable to store bond order information and thus explicit hydrogen assignments are frequently incomplete or incorrect. Consequently, the Molegro Molecular Viewer was used to assign bond orders, correct bonds, hybridization and charges. During the protein preparation procedure, water molecules that were present in the crystal structure were removed.

2.5 Molecular Docking:

The docking analysis was carried out by utilising Python Prescription (PyRx) 0.8 virtual screening tool along with BIOVIA Discovery Studio Visualizer (DS 2021). It is necessary to initially convert the updated receptor file from PDB to PDBQT file format before proceeding. All the converted receptor and ligands were uploaded to the workspace of PyRx and minimization was done using the Open Babel program. All the receptors were closed in the grid box and all the grid points (i.e. X, Y, and Z axis) were assigned accordingly for docking. Grid box arrangement was carried out at a distance of 1 Å in order to enable the ligand to move freely and find the most suitable location to attach to the amino acid at the most convenient spot of the enzyme. For every single protein-ligand combination, a separate docking study was carried out. The analysis of the molecular docking simulation was acquired from parameter scoring of the affinity energy values. The outcomes were arranged in ascending order of docking energies. Each cluster's lowest binding energy was chosen as representative. The binding affinity in between the receptor and ligand is determined for all binding regions and the result is reported as affinity (kcal/mol).

2.6 Protein–ligand Interactions:

The visualization of protein-ligand interaction was investigated by utilising the BIOVIA Discovery Studio Visualizer. 3D and 2D arrangement of the interaction was also displayed for the final docking output. Further details from the interaction of protein-ligand can be utilise to understand the nature of hydrophobics and other forms of hydrogen bonds, as well as which amino acids are crucial for bond formation.

2.7 In silico Pharmacokinetic Studies: Pharmacokinetic study is essential to evaluate ADME properties of chemical compounds. The pharmacokinetic properties of chemical constituents were assessed by using the Swiss ADME tool. The molecular configurations of the compounds were uploaded in the form of canonical SMILES in order to predict various pharmacokinetic parameters. The measured parameters include passive gastrointestinal absorption (HIA) and penetration of blood-brain barrier (BBB), which are comprised within the BOILED-Egg model, Cytochromes P450 (CYP450), 24 prediction of skin permeability coefficient (Kp), P-glycoprotein (P-gp), and bioavailability (F) score.

2.8 Prediction of Toxicity:

ProTox-II webserver has been utilised to estimate the ligand's organ toxicities, toxicological endpoints, and LD50. The structure of the active compounds were found by using the compound names in the PubChem. The server analysed the toxicity and selected the toxicity of the targets after choosing the models to be utilised. It was also assessed whether the chemical compounds possess any potentially harmful side effects. Drug induced hepatotoxicity is a type of acute or chronic liver injury and drug withdrawal is a primary reason for hepatotoxicity. The term "Carcinogenicity" describes the induction of tumours in cells by chemicals or we can say a carcinogenic compound has the ability or tendency to cause cancer. Data analysis is done by using two databases: and the CEBS database and the Carcinogenic Potency Database (CPDB).

3. RESULTS AND DISCUSSION:

3.1 Ligand structure preparation:

The phytoconstituents viz. Gallic acid, Vanillic acid, Syringic acid, Caffeic acid, p-Coumaric acid, Quercetin, Catechin, Beta-carotene, Betanin, Tocopherols, valsartan, lisinopril and metoprolol were selected as ligands and the structures of compounds.

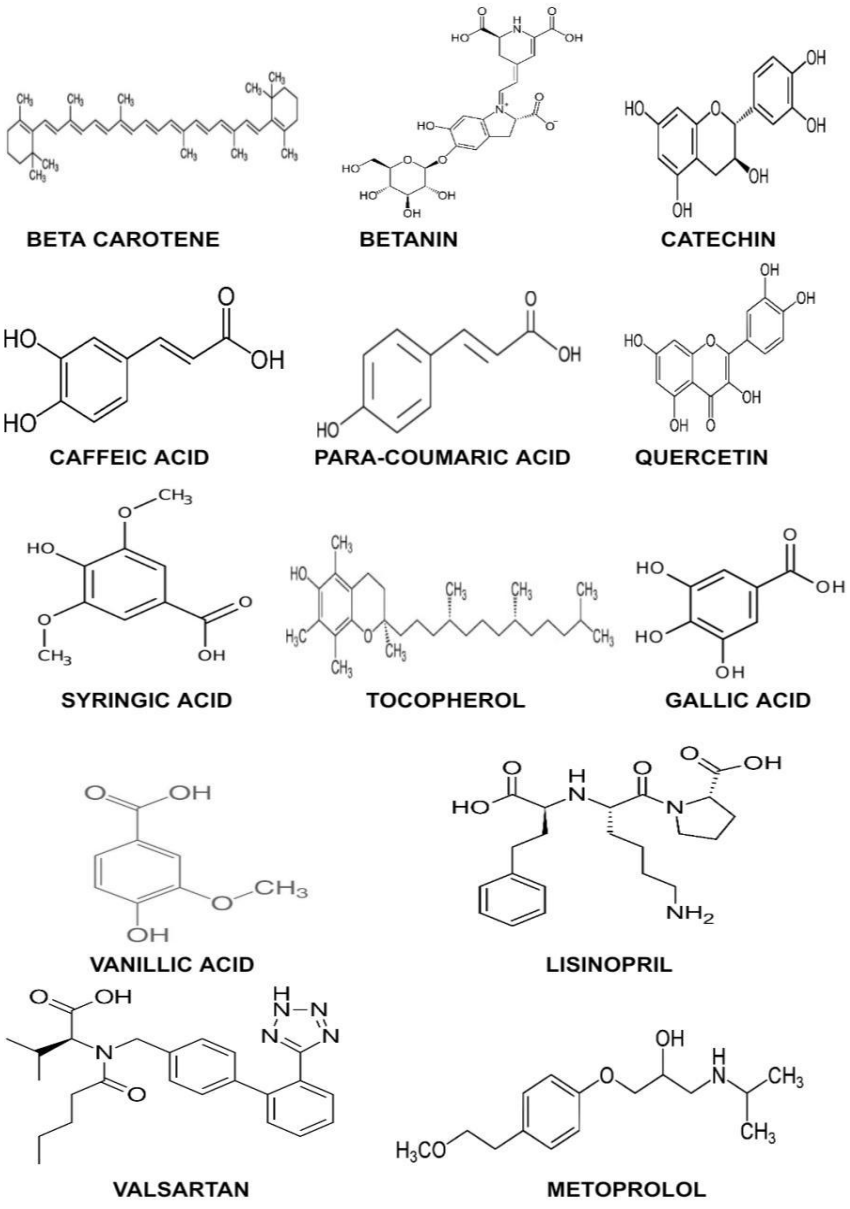


Figure-1: Chemical structure of ligands

Table 1:Displays the canonical SMILES (Simplified molecular input line entry specification) of ligands along with PubChem CID and Molecular formula-

Ligand	SMILES	PubChem CID	Molecular Formula
1.Beta carotene	CC1=C(C(CCC1)(C)C)/C=C/C(=C/C=C/C(=C/C=C/C=C(/C=C/C=C(/C=C/C2=C(CCCC2(C)C)C)\C)\C)/C)/C	5280489	$C_{40}H_{56}$
2. Betanin	C1[C@H](N=C(C=C1/C=C/N2[C@@H](CC3=CC(=C(C=C32)O)O[C@H]4[C@@H]([C@H]([C@@H]([C@H](O4)CO)O)O)O)O)C(=O)O)C(=O)O)C(=O)O	6540685	$C_{24}H_{26}N_2O_{13}$
3. Caffeic Acid	C1=CC(=C(C=C1/C=C/C(=O)O)O)O	689043	$C_9H_8O_4$
4. Catechin	C1[C@@H]([C@H](OC2=CC(=CC(=C21)O)O)C3=CC(=C(C=C3)O)O)O	9064	$C_{15}H_{14}O_6$
5.Para-coumaric acid	C1=CC(=CC=C1/C=C/C(=O)O)O	637542	C9H_8O_3
6. Gallic acid	C1=C(C=C(C(=C1O)O)O)C(=O)O	370	$C_7H_6O_5$
7. Quercetin	C1=CC(=C(C=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O)O	5280343	$C_{15}H_{10}O_7$
8. Syringic Acid	COC1=CC(=CC(=C1O)OC)C(=O)O	10742	$C_9H_{10}O_5$
9. Tocopherol	CC1=C(C2=C(CC[C@@](O2)(C)CCC[C@H](C)CCC[C@H](C)CCCC(C)C)C(=C1O)C)C	14985	$C_{29}H_{50}O_2$
10. Vanillic Acid	COC1=C(C=CC(=C1)C(=O)O)O	8468	$C_8H_8O_4$
11. Lisinopril	C1C[C@H](N(C1)C(=O)[C@H](CCCCN)N[C@@H](CCC2=CC=CC=C2)C(=O)O)C(=O)O	5362119	$C_{21}H_{31}N_3O_5$
12. Valsartan	CCCCC(=O)N(CC1=CC=C(C=C1)C2=CC=CC=C2C3=NNN=N3)[C@@H](C(C)C)C(=O)O	60846	$C_{24}H_{29}N_5O_3$
13. Metoprolol	CC(C)NCC(COC1=CC=C(C=C1)CCOC)O	4171	$C_{15}H_{25}NO_3$

3.2 Protein structure Preparation:

The three-dimensional structures of the targeted receptor proteins associated with lipid metabolism were obtained from protein data bank. In this study 3 selected molecular targets related to Hypertension, explained below-

3.2.1 Angiotensin-Converting Enzyme Inhibitors Receptor -

The most frequently employed drugs for treatment of hypertension are Angiotensin-Converting Enzyme Inhibitors, also known as ACE Inhibitors. These drugs mostly worked by inhibiting the conversion of angiotensin I to angiotensin II. Thus the drugs inhibit tubular sodium,calcium reabsorption, aldosterone secretion and arteriolar vasoconstriction. Thus, the drugs reduce hypertension. From the protein data bank,ace inhibitor receptor, PDB ID- 1O86(with the resolution of 2.0Å) was retrieved. The 3D structure of targeting receptor-

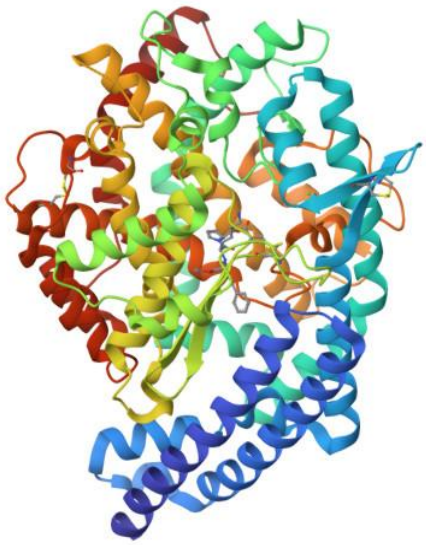


Figure 2: 3D structure of Angiotensin-Converting Enzyme Inhibitors Receptor

3.2.2 Angiotensin (AT_1) receptor -

Angiotensin (AT1) receptor blockers are medications primarily used to treat hypertension. There are two types of angiotensin receptors AT_1 and AT_2 receptors.The drugs have high binding affinity for AT1 receptor compared to AT2 receptor. Bhai blocking the AT1 receptor drugs block the effects of angiotensin II. Thus, the drugs help to treat hypertension. The protein, PDB ID - 7BM1(with the resolution of 1.37Å) was downloaded from protein data bank. The 3D structure of targeted receptor -

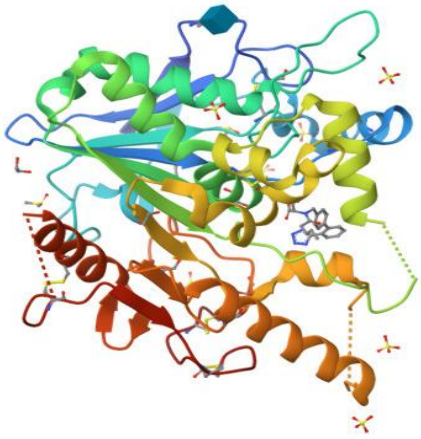


Figure 7: 3D structure of Angiotensin (AT1) receptor

3.2.3 Beta Adrenergic receptor -

The drugs of Beta blockers are effective in all grades of hypertension. There are two types of Beta blockers-Beta 1 receptor which primarily present in the heart kidney and it regulates heart rate and renin release. Beta 2 receptor which are found in lungs, blood vessels, smooth muscles and stimulation causes relaxation of smooth muscles, bronchodilation and vasodilation. Drugs bind both receptors and decrease sympathetic out flow resulting in decreased heart rate,force of contraction and cardiac output. Drugs also decrease renin release resulting in decreased BP. From the protein data bank,3D structure of targeted protein PDB ID - 6PS5(with the resolution of 2.90Å) was obtained.

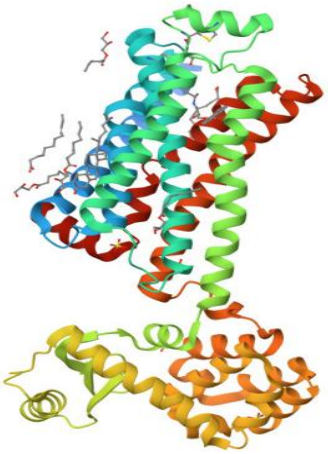


Figure 3: 3D structure of Beta-Adrenergic receptor

3.3 Molecular docking:

3.3.1 Docking Analysis of Angiotensin-Converting Enzyme Inhibitors Receptor:

Docking simulation of active compounds from Selenicereus undatus against ACE receptor shows that Beta carotene and Betanin have the highest affinity of (-11.0 kcal / mole) and (- 10.0 kcal / mole) which have more negative compared to standard ligand Lisinopril (-7.4 kcal / mole). Gallic acid shows the lowest binding affinity with a docking score of (-6.0 kcal / mole). Quercetin (-8.3 kcal / mole), Catechin (-7.9 kcal / mole), Caffeic acid (-6.4 kcal / mole), para coumaric acid (-6.2 kcal / mole), Syringic Acid (-6.3 kcal / mole), Tocopherol (-6.9 kcal / mole) and Vanillic acid (-6.1 kcal / mole) showed binding affinity towards the receptor.

Table 2: Represents docking interaction of ACE receptor with active compounds of *Selenicereus undatus* and synthetic ligand

Ligands	Binding affinity (kcal / mole)	Interaction with Amino acids
1.Beta carotene	-11.0	HIS A-383,PHE A-457,VAL A-379,LYS A-449,LEU A-375,TYR A-287.
2.Betanin	-10.0	ASN A-85, ARG A-124, LEU A-139, GLU A-143, ARG A-522, TYR A-523, GLU A-143, ARG A-522, TYR A-523, GLU A-411, GLU A-384, HIS A-353.
3.Caffeic acid	-6.4	TRP A-220,ILE A-204,TYR A-135,ARG A-124,glu A-123, SER A-219.
4.Catechin	-7.9	VAL A-379, ASP A-453, LYS A-454.
5.Gallic acid	-6.0	ARG A-124, GLU A-123, ALA A-207, ILE A-204, ASN A-211.
6.P-coumaric acid	-6.2	GLU A-411, GLU A-403, PRO A-407, MET A-223, PHE A-570
7.Quercetin	–8.3	ASP A-453, LYS A-454, VAL A-379, GLN A-281, TYR A-520, TYR A-523, ALA A-354.
8.Syringic acid	-6.3	LEU A-81, ASN A-170, LEU A-140.
9.Tocopherol	-6.9	MET A-223, GLY A-404, PRO A-407, GLU A-403, TYR A-360, PHE A-391, ALA A-356, HIS A-387.
10.Vanillic Acid	-6.1	ARG A-124, ALA A-207, ILE A-204, ASN A-211, TRP A-220.
11.Lisinopril	-7.4	VAL A-379, GLU A-376, LEU A-375, ASN A-285, ALA A-170, THR A-301, ASP A-288.

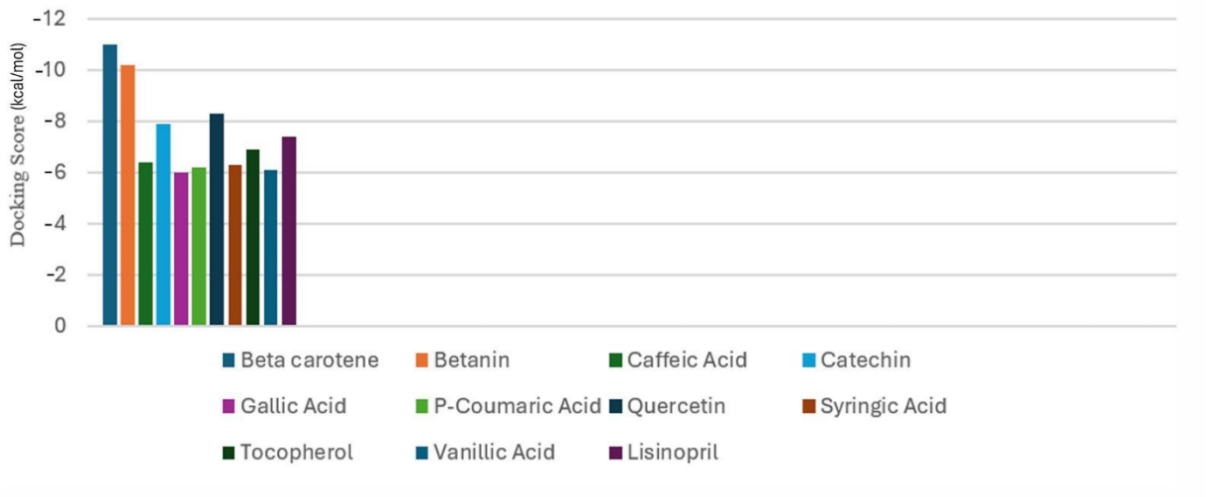
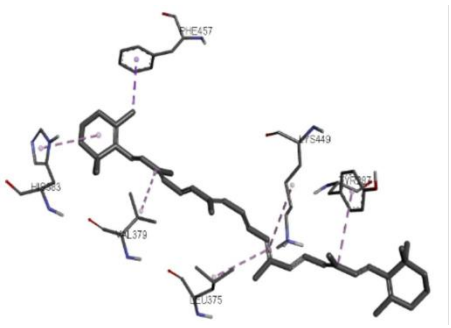
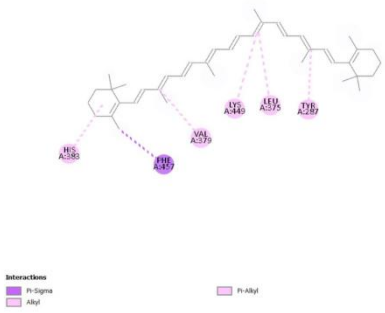
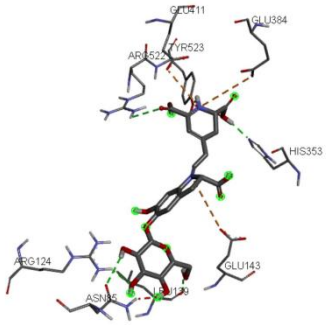
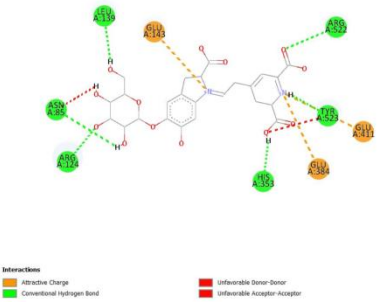
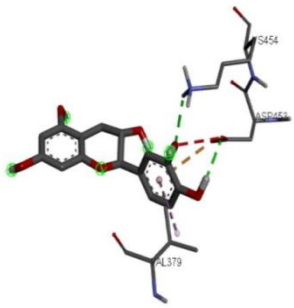
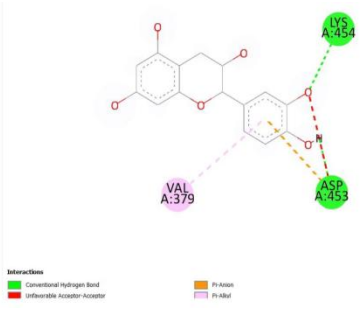
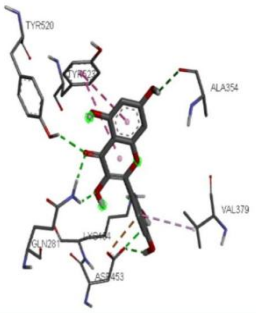
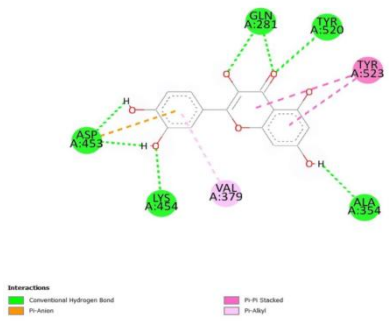
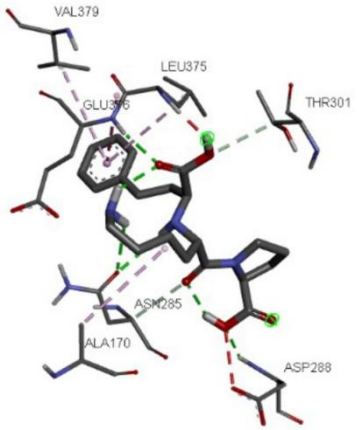
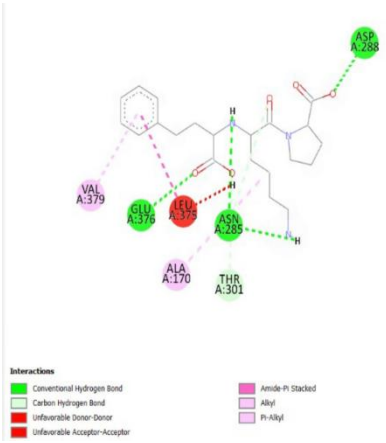


Figure 5: Binding affinity of ACE receptor with active compounds and synthetic ligand

Table 3: 3D and 2D structure of the higher binding affinities of active constituents and binding ligand on ACE receptor -

CHEMICAL CONSTITUENTS	3D STRUCTURE	2D STRUCTURE
1.Beta carotene		
2.Betanin		
3.Catechin		

4.Quercetin		
5.Lisinopril (standard)		

3.3.2 Docking Analysis of Angiotensin (AT1) receptor

In the characteristic binding to AT1 receptor, all the reported compounds were found to have potential binding affinity. The target prediction suggests that Beta carotene has highest binding affinity value of (-9.2 kcal / mole) which is more negative compared to standard ligand Valsartan (-8.8 kcal / mole) and Vanillic acid shows the lowest binding affinity value of (-5.6 kcal / mole). In addition,Quercetin (-7.6 kcal / mole), Catechin (-7.3 kcal / mole), Caffeic acid (-6.5 kcal / mole),para coumaric acid (-6.6 kcal / mole), Betanin (-8.5 kcal / mole), Tocopherol (-8.1 kcal / mole), Syringic acid (-6.0 kcal / mole) and Gallic acid(-5.8 kcal / mole) showed binding affinity towards the receptor.

Table 4: Represents docking interaction of AT1 receptor with active compounds of *Selenicereus undatus* and synthetic ligand-

Ligands	Binding affinity (kcal / mole)	Interaction with Amino acids
1.Beta carotene	-9.2	ARG A-139,MET A-143, TRP A-128, TYR A-129, PHE A-268, ILE A-291, PHE A-320.
2.Betanin	-8.5	TRP A-128, TYR A-129, CYS A-130, PHE A-268, ALA A-233.
3.Caffeic acid	-6.5	PHE A-320, ILE A-291, PHE A-268, PHE A-319.
4.Catechin	-7.3	VAL A-346, TRP A-128, ILE A-291, PHE A-268, PHE A-319.
5.Gallic acid	-5.8	PHE A-268, VAL A-346, GLN A-343.
6.P-coumaric acid	-6.6	ILE A-291, PHE A-320.
7.Quercetin	-7.6	TRP A-128, ALA A-342, VAL A-346, ILE A-291, TYR A-129.
8.Syringic acid	-6.0	ARG A-244, LEU A-328, ASP A-243, PRO A-303, THR A-327, ARG A-305, GLU A-247, ARG A-329.
9.Tocopherol	-8.1	PHE A-268, TRP A-128, PHE A-131, TYR A-129.
10.Vanillic Acid	-5.6	GLN A-343, ILE A-291, VAL A-346, PHE A-268.
11.Valsartan	-8.8	PHE A-268, VAL A-346, PRO A-287, ILE A-291, TRP A-128, TYR A-129.

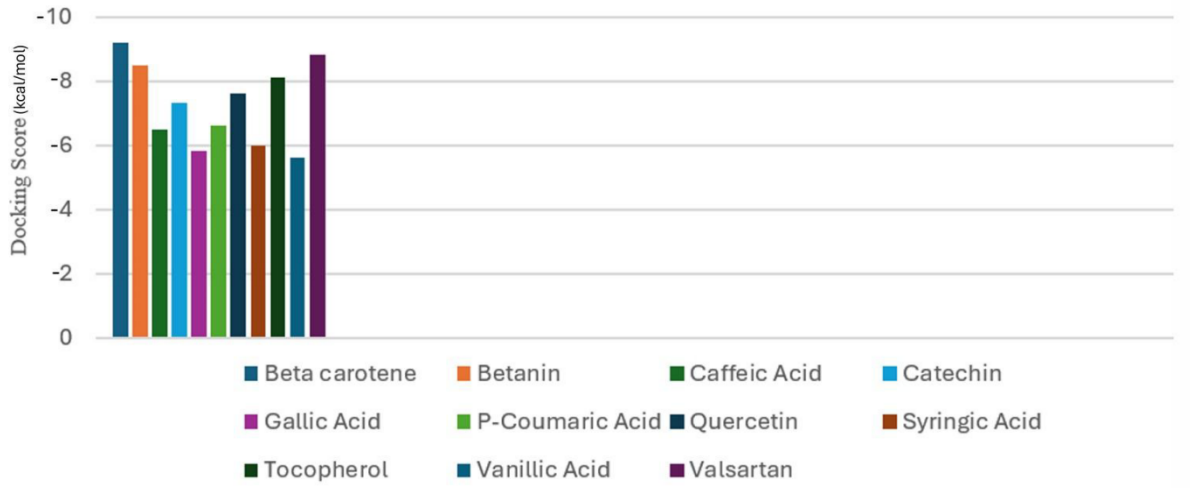
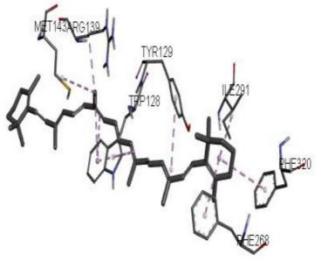
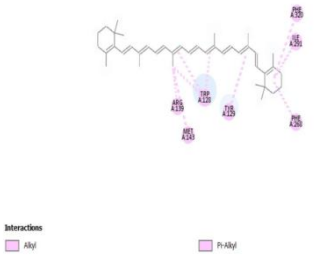
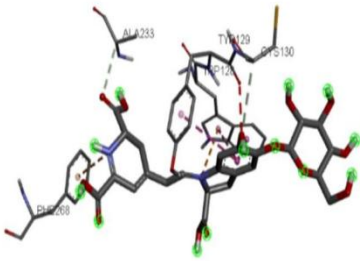
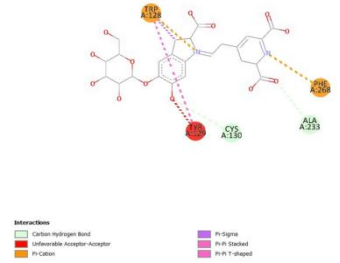
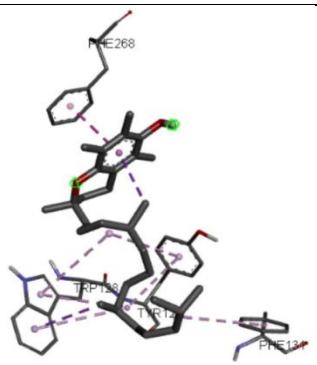
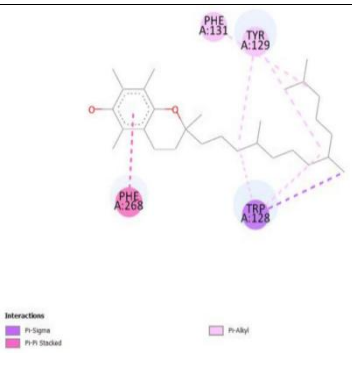
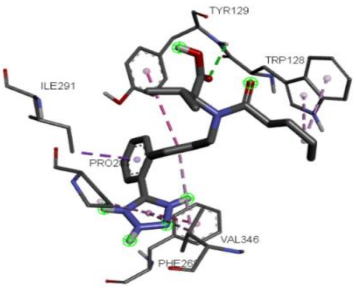
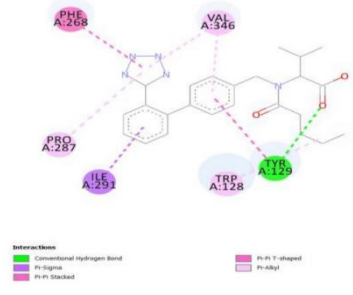


Figure 5: Binding affinity of AT1 receptor with active compounds and synthetic ligand

Table 5: 3D and 2D structure of the higher binding affinities of active constituents and binding ligand on AT1 receptor –

CHEMICAL CONSTITUENTS	3D STRUCTURE	2D STRUCTURE
1.Beta carotene		
2.Betanin		
3.Tocopherol		
4.Valsartan **(standard)**		

3.3.3 Docking Analysis of Beta-Adrenergic receptor -

In these docking studies have revealed that Beta carotene (-9.0 kcal / mole), Betanin (-8.1 kcal / mole), Quercetin (-7.7 kcal / mole) and Tocopherol (-7.7 kcal / mole) have more negative binding affinity compared to the reference ligand Metoprolol (-5.9 kcal / mole). Syringic acid has the lowest binding affinity of (-5.3 kcal / mole). In addition, Caffeic acid (-5.6 kcal / mole), Catechin (-7.4 kcal / mole), Gallic acid (-6.3 kcal / mole), p-Coumaric acid (-7.1 kcal / mole) and Vanillic acid (-5.7 kcal / mole) showed binding affinity towards the receptor.

Table 6: Represents docking interaction of Beta-Adrenergic receptor with active compounds of *Selenicereus undatus* and synthetic ligand-

Ligands	Binding affinity (kcal / mole)	Interaction with Amino acids
1.Beta carotene	-9.0	TYR A-70, TRP A-158, LEU A-115, PHE A-166.
2.Betanin	-8,1	ASP A-1070, LEU A-1032, GLU A-1022, ASP A-1020, ARG A-1145, GLN A-1105.
3.Caffeic acid	-5.6	LYS A-305, ARG A-304, TYR A-308, ASN A-293, THR A-195.
4.Catechin	-7.4	GLU A-1011, GLN A-1105, GLU A-1022, ARG A-1145, ASP A-1020.
5.Gallic acid	-6.3	VAL A-114.
6.P-coumaric acid	-7.1	SER A-203, PHE A-289, VAL A-114, VAL A-117, ASP A-113.
7.Quercetin	-7.7	SER A-329, ASP A-331, ASN A-69, LYS A-270, PRO A-330, ALA A-271.
8.Syringic acid	-5.3	THR A-68, ASN A-69, ALA A-271.
9.Tocopherol	-7.7	VAL A-160, VAL A-157, LEU A-145, PHE A-133, ILE A-153, VAL A-129, TRP A-122, VAL A-126.
10.Vanillic Acid	-5.7	HIS A-93, ASP A-192, TYR A-316, TRP A-109, TRP A-313.
11.Metoprolol	-5.9	TRP A-109, CYS A-191, LYS A-305, PHE A-194.

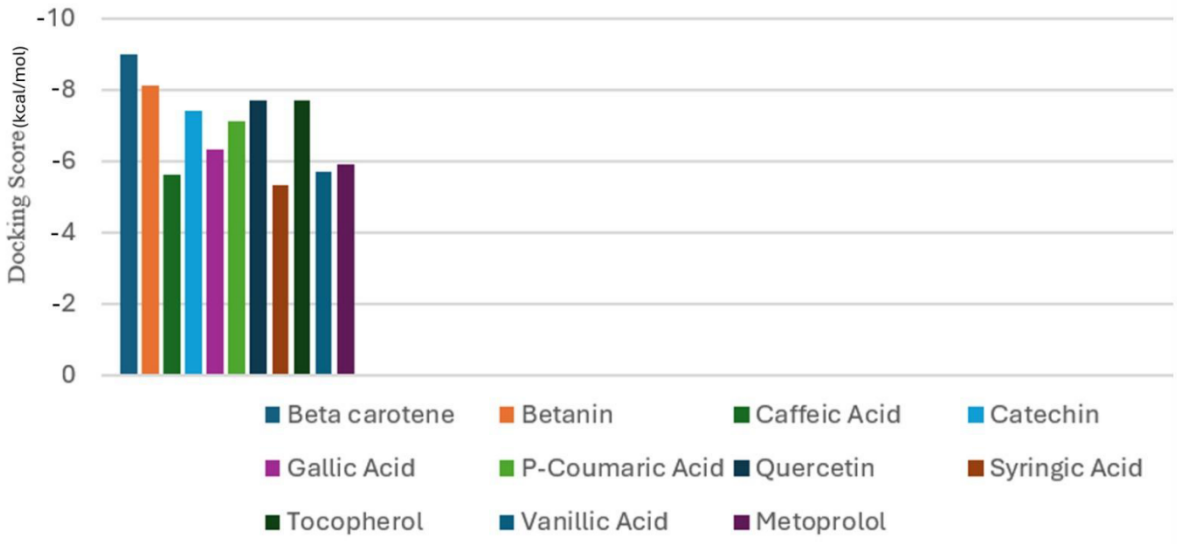
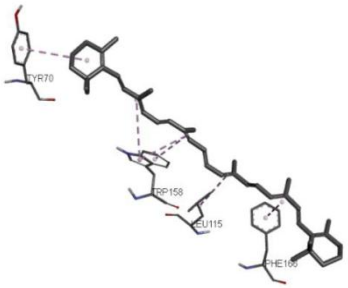
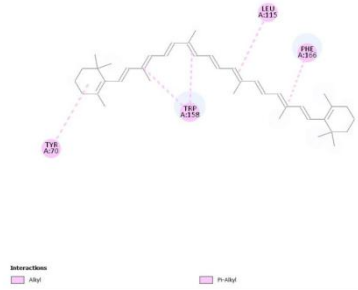
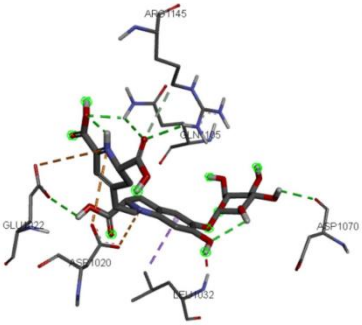
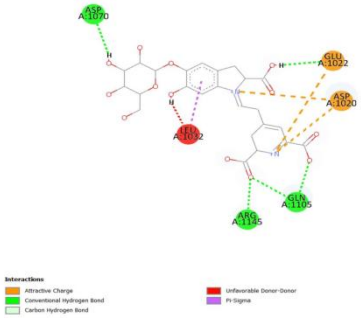
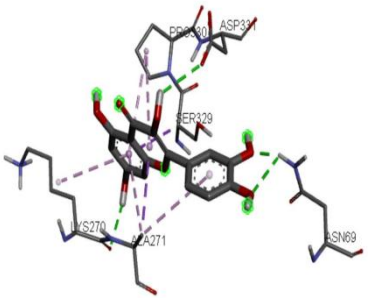
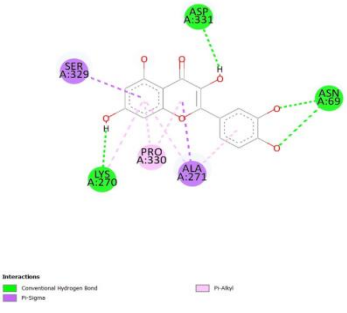
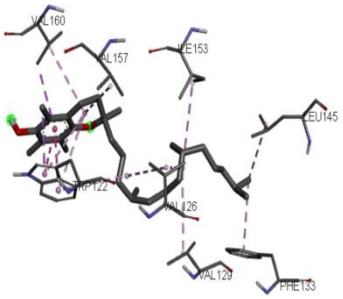
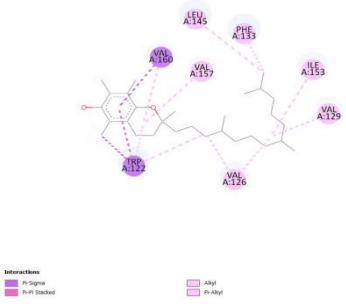
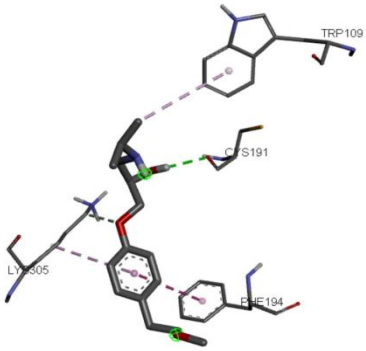
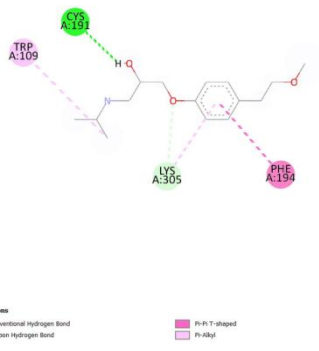


Figure 6: Binding affinity of Beta-Adrenergic receptor with active compounds and synthetic ligand.

Table 7: 3D and 2D structure of the higher binding affinities of active constituents and binding ligand on Beta Adrenergic receptor -

CHEMICAL CONSTITUENTS	3D STRUCTURE	2D STRUCTURE
1.Beta carotene		
2.Betanin		
3.Quercetin		
4.Tocopherol		
5.Metoprolol (standard)		

3.4 In silico Pharmacokinetic Studies:

The overall in silico pharmacokinetics predictions showed high GI absorption for all ligands except Beta carotene Betanin and Tocopherol. The blood brain permeability was observed for Para-coumaric acid and Metoprolol. In this study, Betanin, Catechin, Gallic acid, Para-coumaric acid, Caffeic acid, Quercetin, Syringic acid, Vanillic acid and standard drugs like Lisinopril, Valsartan and Metoprolol showed higher negative Log kp value except Beta carotene and Tocopherol showed lower negative kp value. Beta carotene, Catechin, Tocopherol and sympathetic ligand Lisinopril showed p-glycoprotein substrate activity. To detect inhibitory activity for cytochrome p450 as CYP1A2 all phytoconstituents showed non-inhibitors except Quercetin, for CYP2C19 and CYP2C9 all phytoconstituents showed non-inhibitors except synthetic ligands Valsartan, for CYP2D6 all phytoconstituents showed non-inhibitors except Quercetin and Metoprolol, for CYP3A4 all ligands were observed non-inhibitors except Gallic acid, Quercetin and Valsartan. Bioavailability of Caffeic acid, Catechin, Gallic acid, Quercetin, Tocopherol, Syringic acid, Lisinopril Valsartan and Metoprolol are the same (i.e. 0.55). Bioavailability of Para-coumaric acid and Vanillic acid is the same (i.e. 0.85).

Table 8: ADME analysis of selected ligands along with selected standard drug using Swiss ADME tool-

Ligands	GI ABSORPTION	BBB Permeant	Pgp Substrate	CYP1A2 Inhibitor	CYP2C19 Inhibitor	CYP2C9 Inhibitor	CYP2D6 Inhibitor	CYP3A4 Inhibitor	Log Kp(cm/s)	Bioavailability
1.Beta carotene	↓	–	+	–	–	–	–	–	**-2.90**	**0.17**
2. Betanin	↓	–	–	–	–	–	–	–	**-10.5**	**0.11**
3. Caffeic Acid	↑	–	–	–	–	–	–	–	**-6.58**	**0.56**
4. Catechin	↑	–	+	–	–	–	–	–	**-7.82**	**0.55**
5.Para-coumaric acid	↑	+	–	–	–	–	–	–	**-6.26**	**0.85**
6. Gallic acid	↑	–	–	–	–	–	–	+	**-6.84**	**0.56**
7. Quercetin	↑	–	–	+	–	–	+	+	**-7.05**	**0.55**
8. Syringic Acid	↑	–	–	–	–	–	–	–	**-6.77**	**0.56**
9. Tocopherol	↓	–	+	–	–	–	–	–	**-1.33**	**0.55**
10. Vanillic Acid	↑	–	–	–	–	–	–	–	**-6.31**	**0.85**
11. Lisinopril	↑	–	+	–	–	–	–	–	**-10.8**	**0.55**
12. Valsartan	↑	–	–	–	+	+	–	+	**-5.84**	**0.56**
13. Metoprolol	↑	+	–	–	–	–	+	–	**-6.60**	**0.55**

Note: High-↑, low-↓, yes-(+), no-(-)

3.5 Prediction of Toxicity:

The toxicity was estimated on the basis of several targets that are connected to unfavorable drug reactions. All the compounds have shown negative Hepatotoxicity, Cardiotoxicity and Cytotoxicity. Although Beta carotene and standard drugs, Lisinopril and Valsartan are found to have Neurotoxicity. Phytochemicals like Betanin, Catechin, Gallic acid, Quercetin, Tocopherol and Standard drugs like Lisinopril and Metoprolol have the Respiratory toxicity effect. Compounds like Caffeic acid, Para-coumaric acid, Gallic acid are shown Carcinogenicity. Beta carotene and Quercetin have the effect of Mutagenicity. Most compounds have the toxicity class of 4 and 5 but Catechin and Lisinopril have class 6 toxicity respectively.

Table 9: Toxicity analysis of ten selected ligands along with three synthetic drugs using Pro Tox II-

Ligands	HT	NT	RT	CT	CG	MG	CYT	ARO	AR	HSE	MMP	PP53	LD 50	T CLASS
1.Beta carotene	–	+	–	–	–	+	–	–	–	–	–	–	1510	4
2. Betanin	–	–	+	–	–	–	–	–	–	–	–	–	305	4
3. Caffeic Acid	–	–	–	–	+	–	–	–	+	–	–	–	2980	5
4. Catechin	–	–	+	–	–	–	–	–	–	–	+	–	10000	6
5.Para-coumaric acid	–	–	–	–	+	–	–	–	–	–	–	–	2850	5
6. Gallic acid	–	–	+	–	+	–	–	–	–	–	–	–	2000	4
7. Quercetin	–	–	+	–	+	+	–	–	–	–	+	–	159	3
8. Syringic Acid	–	–	–	–	–	–	–	–	–	–	–	–	1700	4
9. Tocopherol	–	–	+	–	–	–	–	–	–	–	–	–	5000	5
10. Vanillic Acid	–	–	–	–	–	–	–	–	–	–	–	–	2000	4
11. Lisinopril	–	+	+	–	–	–	–	–	–	–	–	–	8500	6
12. Valsartan	–	+	–	–	–	–	–	–	–	–	–	–	2000	4
13. Metoprolol	–	–	+	–	–	–	–	–	–	–	–	–	1050	4

Note: HT(Hepatotoxicity), NT(Neurotoxicity), RT(Respiratorytoxicity), CT(Cardiotoxicity), CG(Carcinogenicity), MG(Mutagenicity), CYT(Cytotoxicity), ARO(Aromatase), AR(Androgen Receptor), HSE(Heat shock factor response element), MMP(Mitochondrial Membrane Potential), PP53(Phosphoprotein [Tumor Suppressor] p53), TC(Toxicity Class) and Active(+) , Inactive(–).

DISCUSSION:

Modern drug discovery requires evaluating the efficacy of molecules and the molecules ability to effectively reach the desired target site in a reactive state. This process involves conducting cellular, animal and human clinical trials, which are both expensive and potentially hazardous. The estimation of a drug's pharmacokinetic properties i.e. absorption, distribution, metabolism and excretion (ADME) is currently supported by computer-aided drug delivery, this provides fast, reliable and predictive data and supports experimental methods.

In this work,we assessed the ADME and toxicity characteristics of the bioactive phytoconstituents that are found in *Selenicereus undatus*, using the Swiss ADME and Protox-II online tool. Using the Swiss ADME and Protox-II online tool, a total 10 phytoconstituents of *Selenicereus undatus* were examined to investigate various characteristics like pharmacokinetic parameters (Table 13) and toxicity study (Table 14) respectively.

The possible interaction between phytocompounds and proteins would lead to creation of novel treatments of a wide range of pathologies. Based on peculiar characteristics of exhibiting strong functional groups, *Selenicereus undatus* is a compound used in several medical treatments. The present study is revealed that a similar type of observation about interaction with three different protein i.e. ACE receptor, AT1 receptor and Beta-Adrenergic receptor by displaying a notable binding energy difference in comparison with standard drugs Lisinopril, Valsartan and Metoprolol.

ACE inhibitors are the most commonly used antihypertensive drugs. It has been discovered that Beta-carotene and Betanin have the highest binding affinity towards the receptor, the Beta-carotene and Lisinopril shared the same Amino acid residue (VAL A-379 and LEU A-375). According to the in-silico investigation, the active phytochemicals derived from the formulation of *Selenicereus undatus* may have the ability to inhibit ACE synthesis and to reduce high blood pressure.

With the AT1 receptor, we found in the result that Beta-carotene has the highest binding affinity towards the receptor. Beta carotene and Catechin shared the common Amino acid residue (PHE A-268, ILE A-291, TRP A-128) with the standard Valsartan. The in-silico docking study revealed that because of higher binding affinity with AT1 receptor, the phytoconstituents of *Selenicereus undatus* may be used to reduce high blood pressure.

In the case of Beta-adrenergic receptor, the results of Docking studies showed that Beta carotene and Betanin have more negative binding affinity compared to

standard ligand Metoprolol. The process by which a ligand fits into the binding sites appears to be determined by its three-dimensional structure. Overall, the result suggests that phytoconstituents present in *Selenicereus undatus* may be able to reduce high blood pressure.

CONCLUSION:

The prediction of binding affinity, pharmacokinetics and toxicity study revealed that the active phytochemicals of *Selenicereus undatus* can be a promising lead compound for a new drug candidate for antihypertensive phytomedicine. It is reasonable to assume that the phytochemicals *Selenicereus undatus* might have the potential to inhibit the ACE synthesis and inhibit the converting of Angiotensin I to Angiotensin II or have the potential to block the AT1 receptor and Beta-Adrenergic receptor. Further, additional research i.e. in vitro and in vivo trials on the same constituents, is required to confirm the results and the clear picture of mechanism of action by which the medicinal plant demonstrated the antihypertensive effects. In short, the findings strongly support the potential use of phytoconstituents from *Selenicereus undatus* as a medicinal herb that might be taken in daily life to prevent hypertension.

Conflict of Interest: The authors declare no potential conflict of interest concerning the contents, authorship, and/or publication of this article.

Author Contributions: All authors have equal contributions in the preparation of the manuscript and compilation.

Source of Support: Nil

Funding: The authors declared that this study has received no financial support.

Informed Consent Statement: Not applicable.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Ethical approval: Not applicable.

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