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INSIGHTS FROM MOLECULAR DOCKING SIMULATIONS ON VERSATILE PLANT: *CAPPARIS ZEYLANICA*

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ABSTRACT

The recent emergence after covid-19 pandemic major threat to human society will be the lifestyle diseases. As the challenges of finding suitable treatment is not fulfilled till date. The study tries to discover traditional and ayurvedic treatment to mitigate such condition. Here we are focusing the potential uses of plant Capparis zeylanica. The Schrödinger software used for docking. Ligand preparation, protein preparation, grid-glide generation is processed for obtaining docking glide score, the ramachandran plot is essential in structural biology, visualizing amino acids in proteins via psi (ψ) and phi (φ) angles for molecular docking studies. It was found that this plant is versatile and have potential target to treat many cardiovascular diseases. Quercetin, alpha amyrin, beta sitosterol, etc. constituents show optimum glide score (-3 to -7) for adrenergic receptor activity. Study mainly use computational methods to predict and support available literature to give full proof interaction between small active molecule and with target protein to understand the medicinal properties of plant. chemical constituents of natural plant Capparis zeylanica contain various cardiovascular, diabetic, or lifestyle diseases.

Keywords: *Capparis zeylanica, phytochemicals, biological activity, antioxidant, flavonoids, phenolic acid, adrenergic receptor, alpha receptor, glide score.*

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INTRODUCTION

The advancement of traditional drug discovery through molecular docking, molecular modelling, and computational chemistry promises a bright future, proving to be invaluable sources for human medicinal treatment.[1] C. Zeylanica was selected based on ethnomedicinal information, which indicates traditional medical practices recognizing flavonoids for their antioxidant, anti-ulcer, anticancer, anti-diarrheal, anti-inflammatory, and antimicrobial activities.[2]

The genus Capparis, which includes approximately 250 known species, has garnered significant attention for its nutritional and therapeutic potential. Notably, Capparis Ovata, Capparis Spinosa, and Capparis Decidua have been elaborately studied as food items like subji and medicinal properties as potential therapeutic applicant. Traditional uses of these plants involve various parts, including stem bark, stem, leaves, green fruits, and roots, which have been used for both nutritional and medicinal purposes.[3] The therapeutic efficacy of Capparis species is attributed to the presence of bioactive compounds, including natural sugars, natural antioxidants (flavonoids, rutin), terpenoids, minerals, vitamins, alkaloids , minerals, and antimicrobial agents.[4] These components contribute to the diverse medicinal properties exhibited by the extracts of Capparis species[5].

Extracts from various parts of plant have demonstrated a wide range of beneficial effects, such as to treat inflammation, reduce fungal infections, analgesic, to treat elevated blood pressure, anti-asthmatic, anti-tussive, hepatoprotective, anti-cancer, anti-hyperlipidemic and anti-fungal properties.[6]

Given the extensive body of research on the nutritional as well as medicinal power of Capparis species, we produced comprehensive and innovative research on same in this article. This manuscript aims to brush up the existing information and give quality research by examining the food value of the content, phytochemicals, traditional medicinal uses, and biological attributes of key Capparis species.[7] The focus will be on the most Species that are widely cultivated and used, such as C. spinosa, C. decidua and C. ovata. In this research it seeks to provide an in-depth Composition of essential high-value nutrients and bioactive compounds, underscoring the medicinal chemistry and pharmacological, biological and medicinal activities associated with various parts of these significant plant belonging to Capparis family.[8] This research will also identify potential areas for future research, thereby advancing the field and opening new avenues for the utilization of Capparis species in various health-related applications.[9]

MATERIAL AND METHODS

Programs and Devices

The computer-aided examination was conducted using maestro version 10.2.010 and mm share version 3.0.010, release 2015-2, on a windows-x64 platform. Maestro serves as the graphical interface for all Schrödinger's applications, including ligprep, protein preparation, site-map, and grid generation glide-xp dock.[10] the workstation employed was an asus laptop (model laptop-3pcc1jn0) equipped with an intel(r) Celeron(r) n4500 processor running at 1.10ghz, 4.00gb ram, and centos linux as the 64-bit operating system.

Database

The ligand molecules of plant chemical constituents were sourced from verified chemical databases such as PubChem, a comprehensive and widely recognized resource ensuring the authenticity and reliability of the data. Target proteins, including human membrane protein serine/threonine protein kinase (akt1) (7wm2), The membrane protein's t3-i2, a 32-residue protein from the alpha-2a adrenergic activation receptor (1hll), the receptor's signaling protein's alpha epinephrine [GPCR] G protein-coupled a receptor (6kuw), and the protein and the ligands alpha 2a epinephrine receptor in complex with the partial agonist (6kuy) obtained from a Protein structure library with its PDB IDs

Ligand preparation

In maestro 10.2, ligand preparation involves importing the ligand structure and converting ligand molecules of phytoconstituents into 3d structures using the ligprep tool.[11] this process includes checking and correcting the geometry, assigning bond orders, adding hydrogen atoms, and generating possible ionization states, ensuring the ligand is in a suitable form for docking simulations and other computational analyses for efficient molecular docking studies and structure-based drug design.[12]

Protein formulation

For molecular docking, the "target protein" was sourced from the RCSB Protein library [PDB]. The Schrödinger Maestro software (version 11.1) was utilized, specifically the Protein Preparation Wizard, to refine the 3-Dimentional structure of the proteins.[13] This preparation involved assigning bond orders, adding hydrogen atoms, utilizing the CCD database, creating zero-order bond relationship to metals and disulfide bonds, and Eliminating water molecules located more than 5 Å away from heteroatom groups.[14] The heteroatom Situations were maintained at a default pH. of 7.0±2.0 using epic. The final step was a constrained minimization using the OPLS3 force field to ensure that heavy atoms convert to an RMSD of 0.30 Å.[15] Generally, protein preparation in Maestro 10.2 involves importing the protein structure, optimizing its geometry, assigning bond orders, adding hydrogen atoms, and generating any missing side chains or loops, followed by energy minimization to refine the structure for molecular docking and simulations.[16] By removing water molecules effectively, entropy of the target molecules is minimized, resulting in a more controlled and stable environment for molecular interactions.[17]

Active site examination and grid generation

Active site examination is crucial in molecular screening and involves using tools like sitemap to analyze entire protein molecules and identify active sites.[18] this analysis predicts active site residues, their volume, and scores. The chosen active site is then used to generate a grid for further study.[19] ligand binding cavities are identified from target molecules, and selected ligands are docked using grid-based ligand docking, such as glide. Docking occurs at the central point of the binding cavity grid box, defined by coordinates x: 5.4; y: 3.70; z: 20.85.

Molecular docking

Molecular docking using maestro 10.2 involves importing the prepared protein and ligand structures, defining the active site or binding cavity on the protein, setting up docking parameters such as grid generation, and performing the docking simulation using algorithms like glide.[20] the software evaluates the interactions between the protein and ligand, generating docking scores and poses that indicate the binding affinity and potential binding modes. post-docking analysis may include visualizing the docked complexes, analyzing binding interactions, and refining the poses for further studies or virtual screening purposes.

Ramachandran plot

The Ramachandran plot is an essential tool in structural biology, utilized for visualization the psi (ψ) and phi (φ) angles Concerning amino acid residues in proteins. It plays a significant role in molecular docking by validating protein structures, identifying residues in disallowed regions, and detecting structural errors before docking simulations. It refines protein models, ensuring energetically favorable conformations.[21] the plot aids in understanding protein-ligand interactions, revealing conformational flexibility and enhancing docking accuracy. In homology modelling, it confirms model reliability and guides template selection. Post-docking, it validates protein-ligand complexes, assessing stability and ensuring no distortions. Overall, the Ramachandran plot ensures accurate docking results and deepens understanding of protein-ligand interactions.

Adrenergic receptor activity:

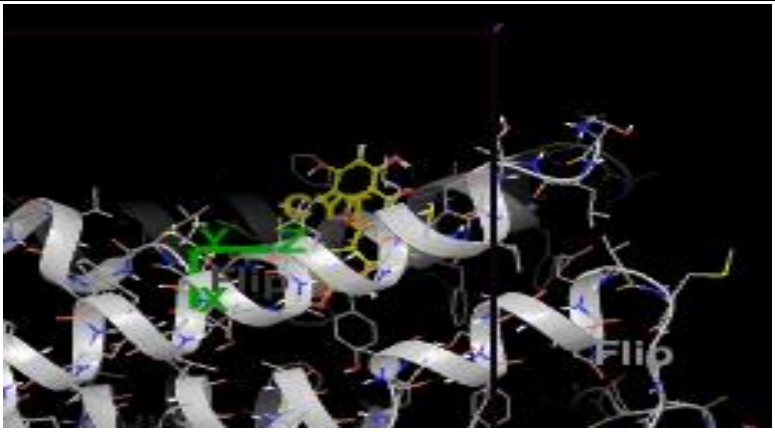
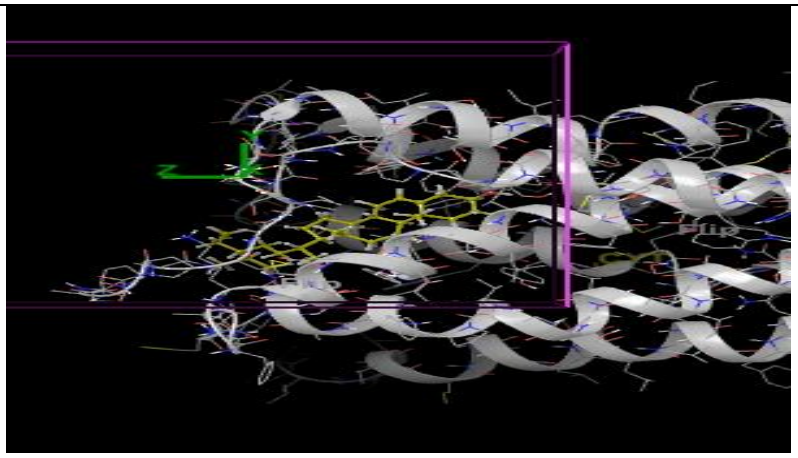
Adrenergic activity showing receptors are a type of G-protein-coupled receptors [GPCR] targeted by catecholamine's like adrenaline and noradrenalin. These receptors are crucial to the sympathetic nervous system, mediating responses such as cardiovascular regulation, smooth muscle tone, and metabolic processes.[22] There are several types of adrenergic receptors, including alpha (α) and beta (β) receptors, each with distinct subtypes such as α1, α2, β1, β2, and β3. The activity of these receptors involves agonist binding, which triggers conformational changes and activates intracellular g proteins, leading to a cascade of signaling events and various physiological outcomes. For instance, β1-adrenergic receptor activation in the heart increases heart rate and contractility, while β2-adrenergic receptor activation in the lungs causes bronchodilation. Conversely, α1-adrenergic receptor activation results in vasoconstriction, raising blood pressure. Adrenergic receptor activity can be modulated by antagonists, which block the receptor's ability to bind agonists and inhibit subsequent signaling pathways. This modulation is therapeutically significant for treating conditions such as hypertension, asthma, and heart failure. Advanced techniques like molecular docking study these interactions, aiding in the design of drugs with high specificity and efficacy. Understanding adrenergic receptor activity allows researchers to develop targeted therapies, improving clinical outcomes in cardiovascular and respiratory diseases.[23]

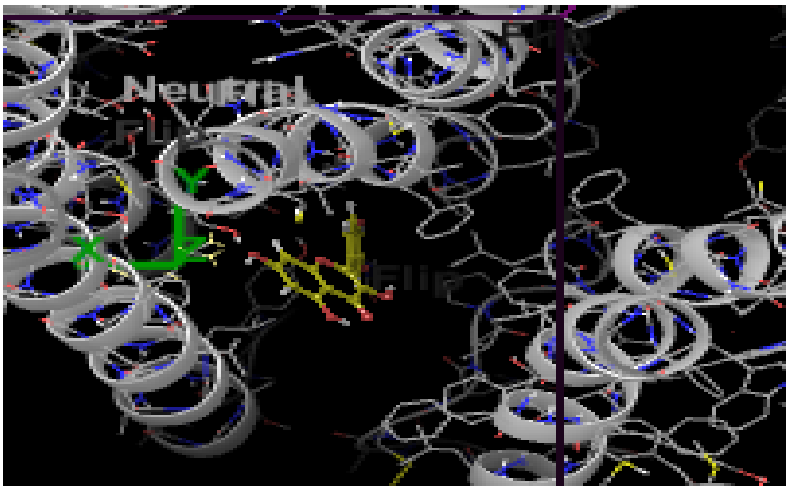
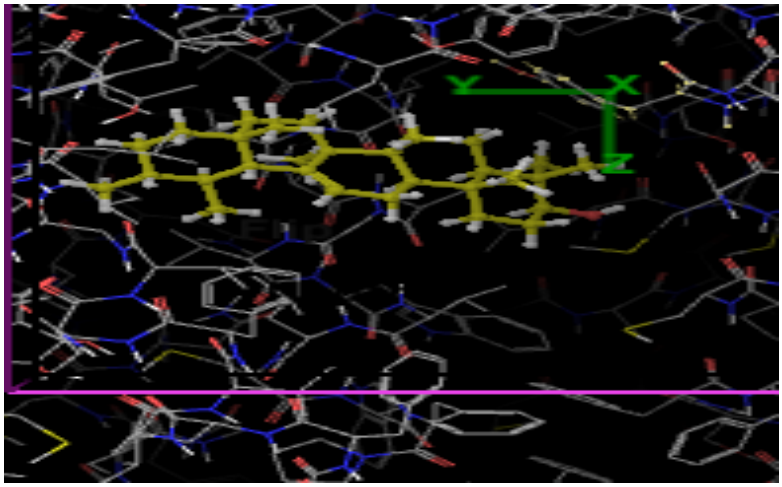
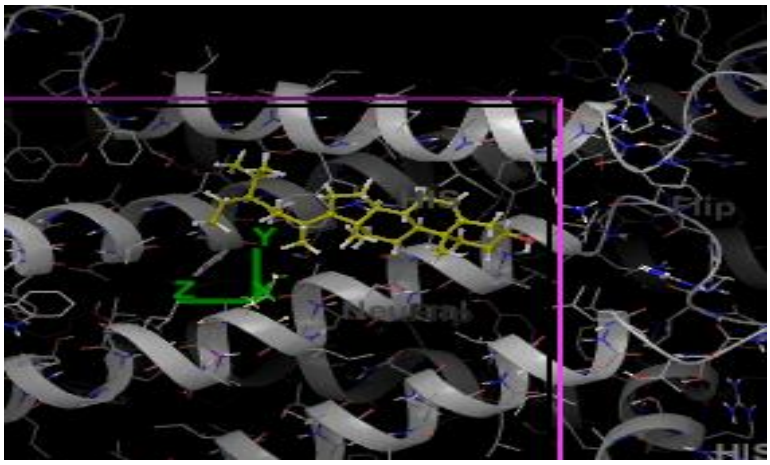
RESULT

The potential binding interaction of all seven compounds of the *Capparis zelynica* have done by Schrödinger molecular docking suites molecular docking studies using glide. Interaction score, glide model and binding energy has been reported in table 1.

Sr. No	Phytoconstituents Name	Molecular Formula	Protein Name	Glide XP score	Binding Energy Score	Glide Model
1	Quercetin	$C_{15}H_{10}O_7$	6kuy	-6.68	-34.18	-49.56
2	Beta-sitosterol	$C_{29}H_{50}O$	6kuy	-4.80	-15.56	-14.43
3	Quercetin	$C_{15}H_{10}O_7$	6kuw	-4.52	-29.97	-47.23
4	Alpha amyrin	$C_{30}H_{50}O$	6kuw	-4.52	-29.97	-38.16
5	Beta-sitosterol	$C_{29}H_{50}O$	6kuw	-4.27	-26.24	-31.67
6	(E)-oct-5-en-7-ynoic acid	$C_8H_{12}O_2$	6kuy	-3.50	-22.19	-27.50
7	Alpha amyrin	$C_{30}H_{50}O$	6kuy	-3.14	-23.39	-27.77

Table No.1.: Interaction score, glide model and binding energy

Sr. No	Compound Name	Protein Pdb id	Ligand-protein interaction
1.	Quercetin	6kuy	 **Fig.1**
2.	Beta-sitosterol	6kuy	 **Fig.2**

3.	Quercetin	6kuw	 **Fig.3**
4.	Alpha amyrin	6kuw	 **Fig.4**
5.	Beta-sitosterol	6kuw	 **Fig.5**

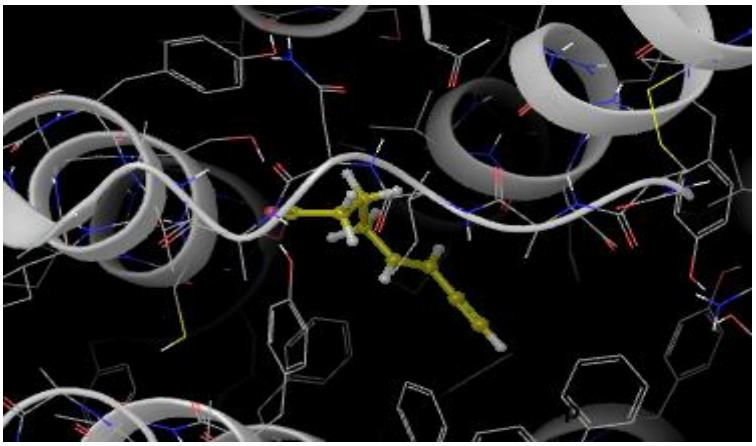
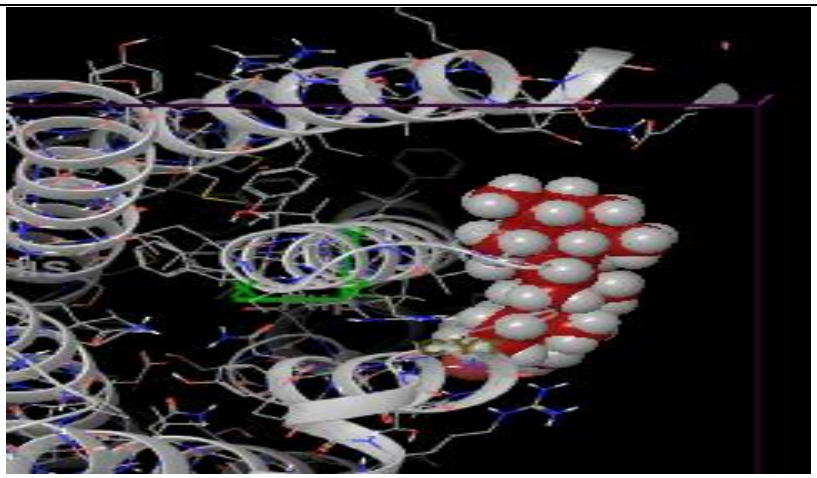
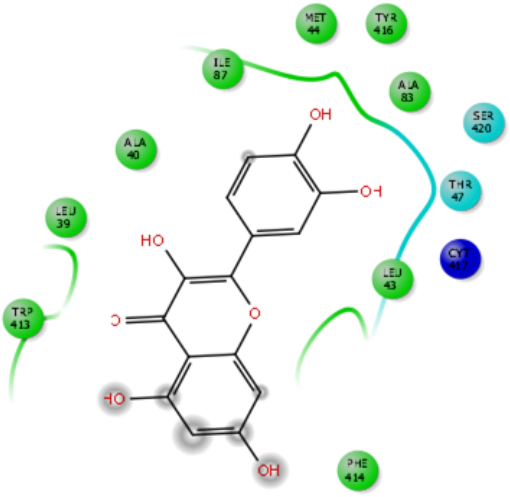
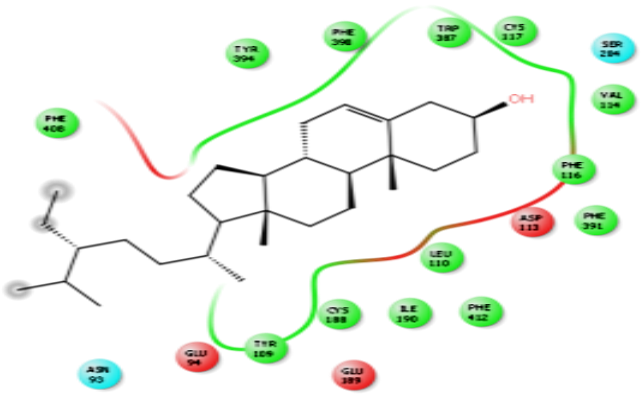
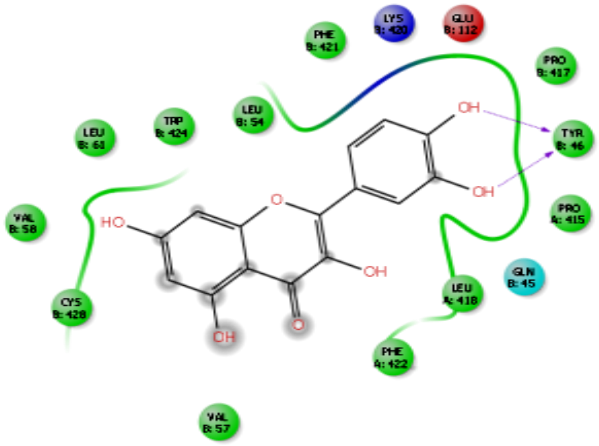
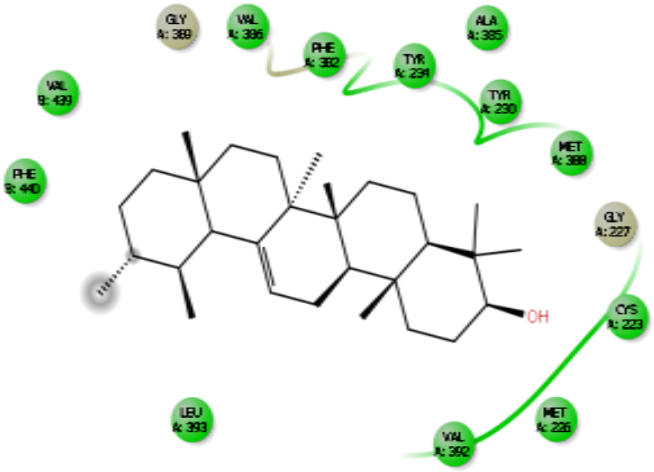
6.	(e)-oct-5-en-7-ynoic acid	6kuy	 **Fig.6**
7.	Alpha amyrin	6kuy	 **Fig.7**

Table No.2.: Ligand-protein interaction

Sr. No	Compound Name	Protein PDB ID	Docking Interaction
1	Quercetin	6kuy	 **Fig.1**

2	Beta-sitosterol	6kuy	 **Fig.2**
3	Quercetin	6kuw	 **Fig.3**
4	Alpha amyrin	6kuw	 **Fig.4**

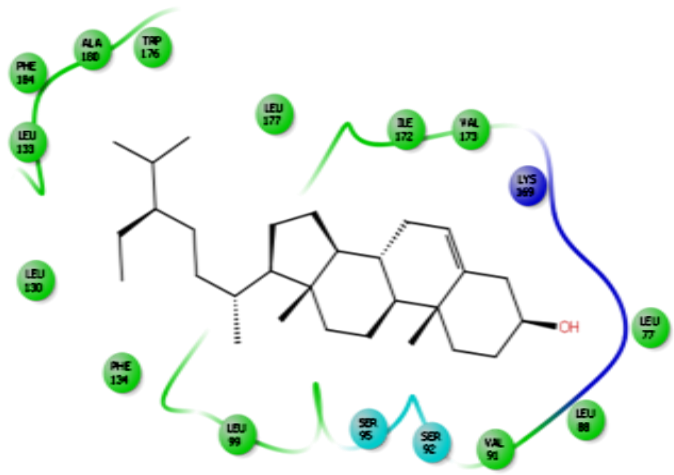
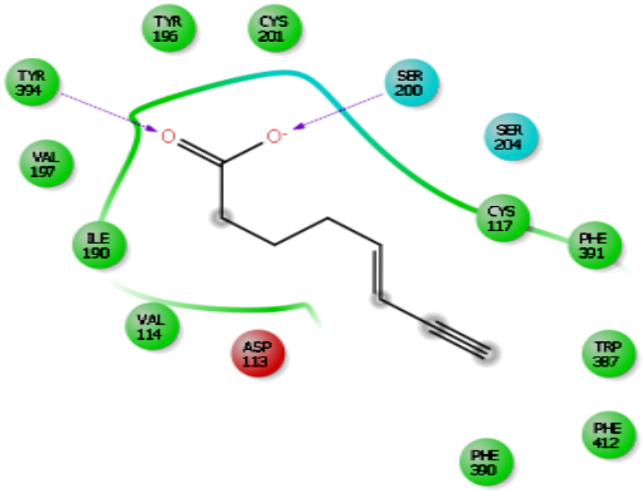
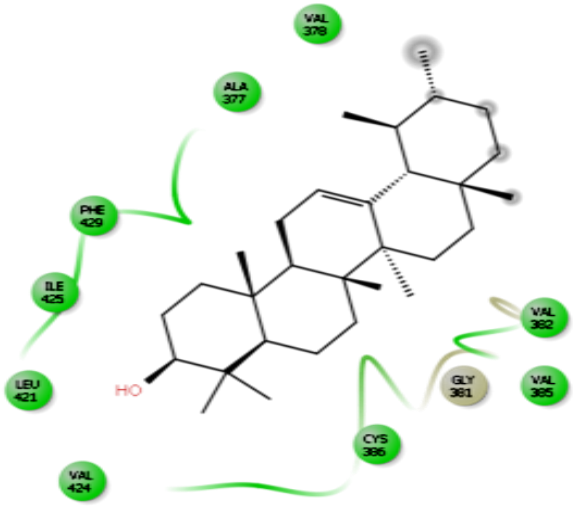
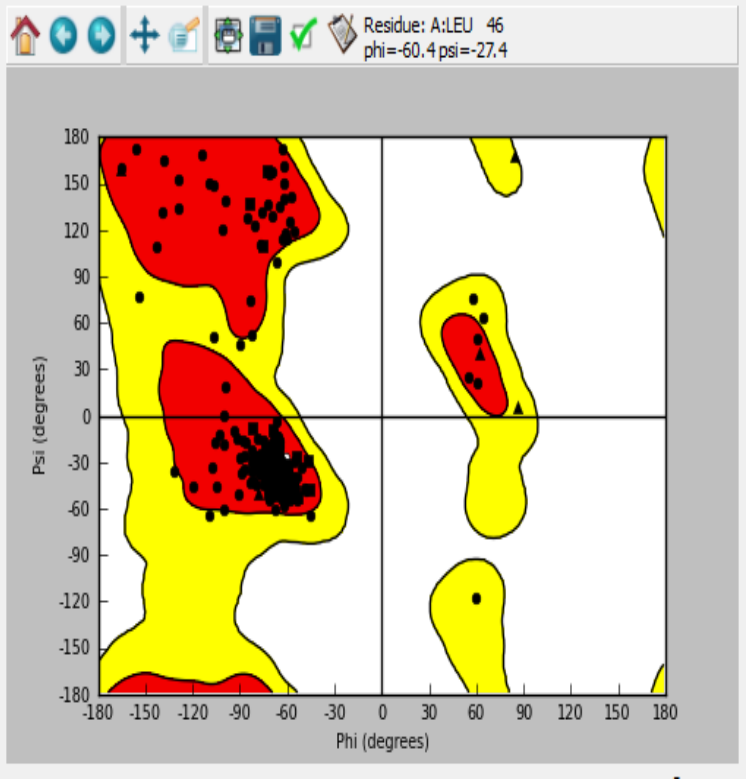
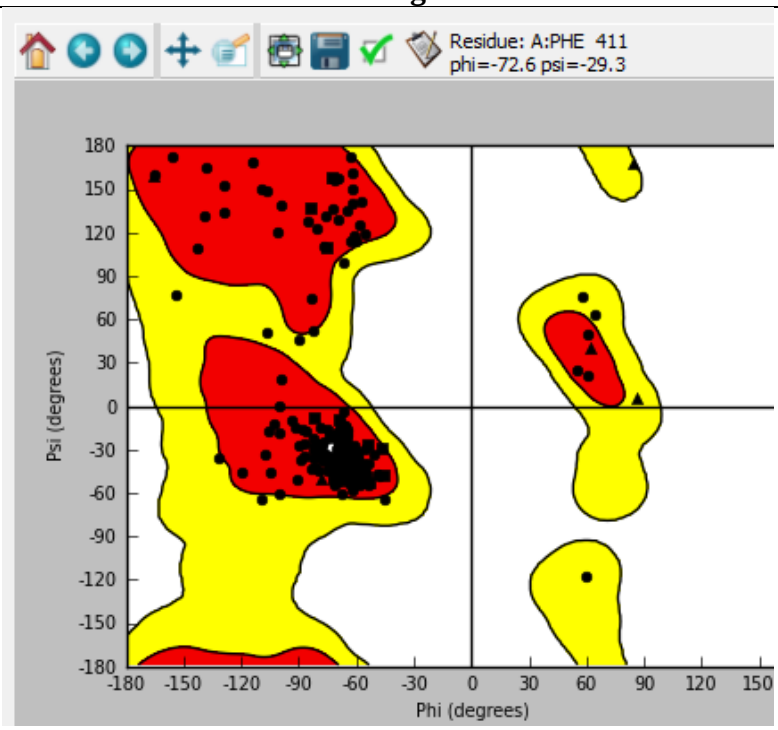
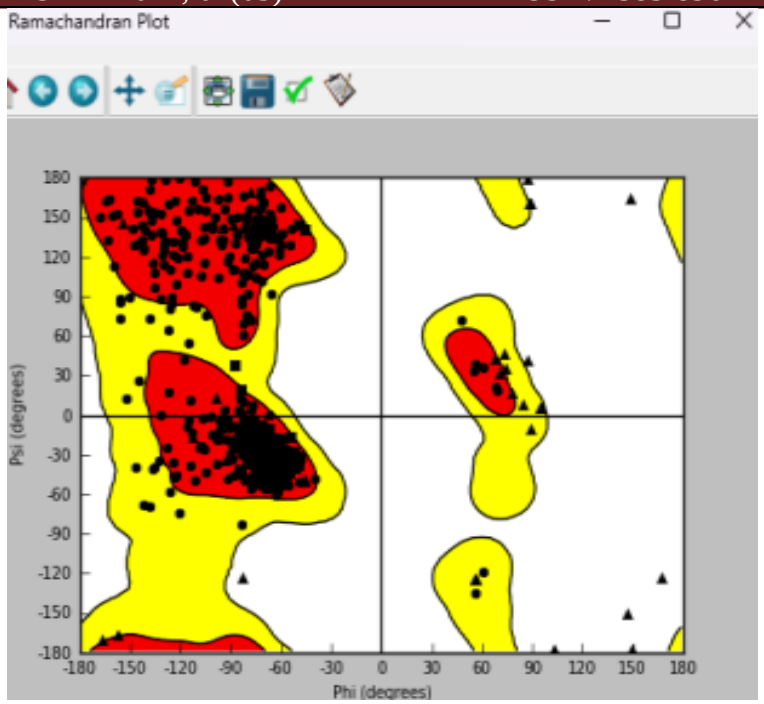
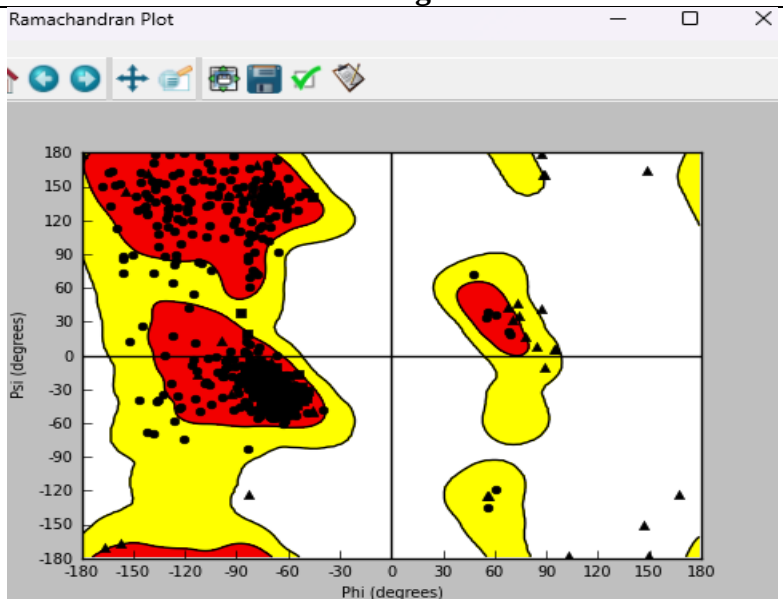
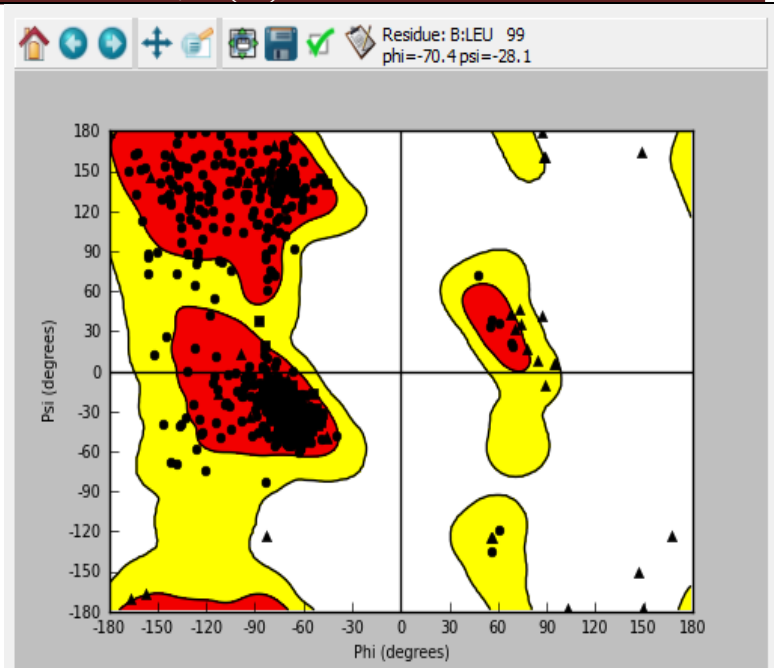
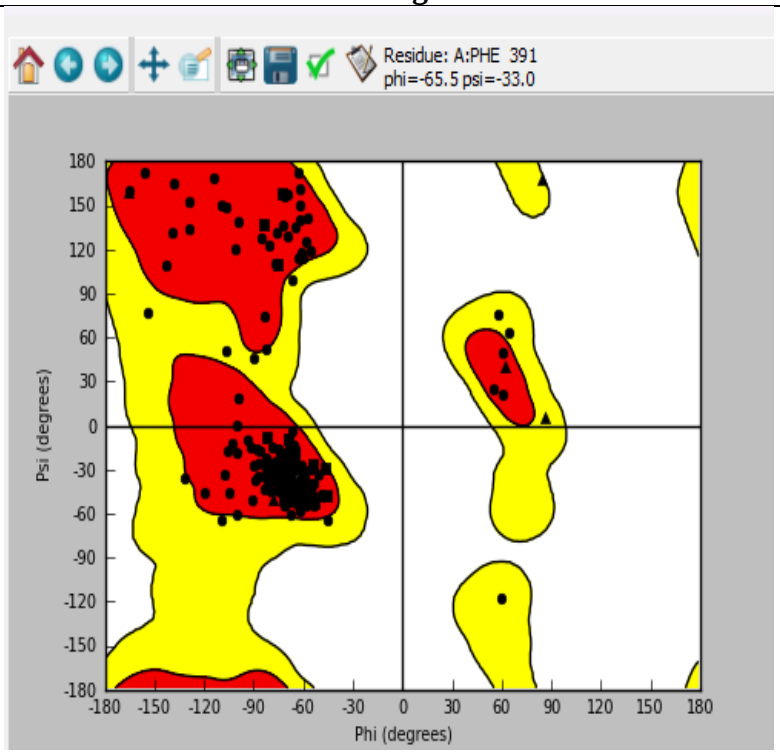
5	Beta-sitosterol	6kuw	 **Fig.5**
6	(E)-oct-5-en-7-ynoic acid	6kuy	 **Fig.6**
7	Alpha amyrin	6kuy	 **Fig.7**

Table No.3.: Docking interaction

Sr. No	Compound Name	Protein PDB ID	Ramachandran plot
1.	Quercetin	6kuy	 **Fig.1**
2.	Beta-sitosterol	6kuy	 **Fig.2**

3.	Quercetin	6kuw	 **Fig.3**
4.	Alpha amyrin	6kuw	 **Fig.4**

5.	Beta-sitosterol	6kuw	 **Fig.5**
6.	(E)-oct-5-en-7-ynoic acid	6kuy	 **Fig.6**

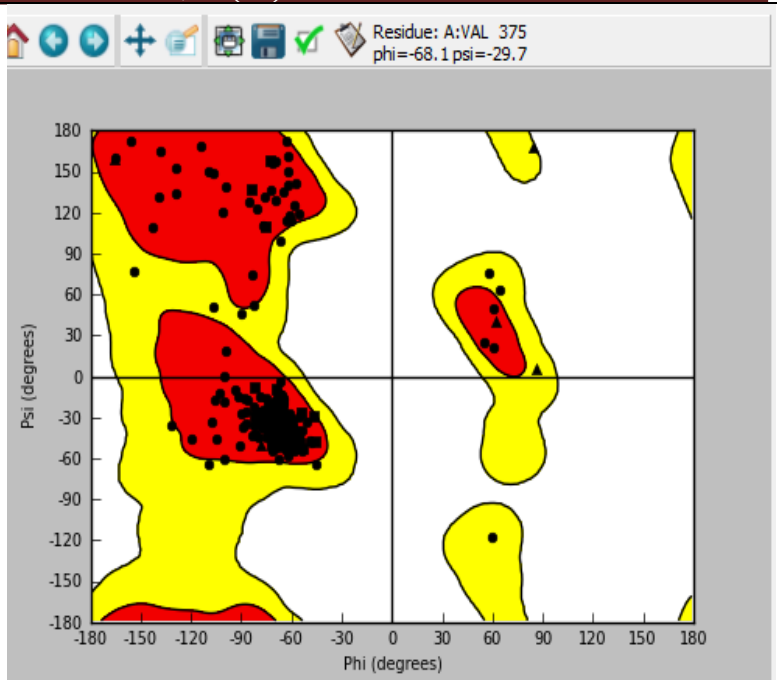
7.	Alpha amyrin	6kuy	

Fig.7

Table 4. Ramachandran plot

DISCUSSION

The docking score in the table reflects potential binding site and favorable binding interaction with target of adrenergic receptor activity. All the standard drugs in the given study are showing potential binding interaction with the target as shown in table 1. Best docked structure has been identified using interaction energy score i.e., Glide emodel and shows best Ligand-target complex orientation. Widely used alpha adrenergic receptor activity showing chemical constituent are the most potent molecule had high score with the target. Quercetin, alpha amyrin, beta-sitosterol, (e)-oct-5-en-7-ynoic acid has better docking score from -3.14 to -6.68. Quercetin is potently active for 6kuy protein. Alpha amyrin is moderately active, active constituent of the Capparis zeylanica having docking score -3.00 to -6.00. All the constituent's quercetin, alpha amyrin, beta-sitosterol, (e)-oct-5-en-7-ynoic acid show consistent interaction with the amino acid residue and these are the strong interaction site of the target. Amino acid residues which have strong interaction with the ligand are shown in table 2.

The pictorial binding interaction of the active constituent are shown in figures in table no.3,4,5. Molecular docking suggests that PHE, LEU is the greatest important amino acid for the hydrophobic interaction and is the greatest important amino acid for the H-bonding interaction. In this study TYR residue is forming h-bond interaction with quercetin, (E)-oct-5-en-7-ynoic acid. Quercetin, beta-sitosterol, (E)-oct-5-en-7-ynoic acid shows consistent polar interaction with SER, THR, ASN, GLN this is the most important for the polar interaction. The Ramachandran plot is showing a graphical Depiction used to visualize dihedral angles ψ against φ of amino acid residues in protein structure. Leu residues typically occupy regions on the Ramachandran plot corresponding to standard secondary structures due to its bulky aromatic side chain, which influences its φ and ψ angles. Leu amino acid in α-helices will have φ angles around -60° and ψ angles around -28° approx. and PHE amino acid in α-helices will have φ angles around -65° and ψ angles around -35° approx. The plot helps to understand the conformational space and sterically allowed regions for these angles, which reflect the protein's secondary structure.

CONCLUSION

Our study concludes that the molecular docking studies revealed that quercetin, beta-sitosterol, alpha amyrine etc. chemical constituents exhibit high binding affinity and selectivity towards adrenergic receptors. These findings suggest that these compounds could serve as potent adrenergic agents, potentially leading to the development of new therapeutic drugs with improved efficacy and reduced side effects. The natural plant Capparis zeylanica have shown adrenergic receptor activity like α1, α2 found that this plant is versatile and have potential target to treat many cardiovascular diseases.

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