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Advances in Bioresearch

ORIGINAL ARTICLE

Molecular Docking Analysis on Phytoconstituents of *Psoralea corylifolia* seeds against Mutant Beta Toxin *Staphylococcus aureus*

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ABSTRACT
Phytochemical analysis of cow urine extracts of Psoralea corylifolia seeds were analyzed by quantitative methods using Liquid Chromatography – Mass spectroscopy (LC-MS). The compounds of seeds from LC-MS analysis and this structure were retrieved from PubChem databases. The phytocompounds are analyzed for drug – likeness as Lipinski's rule. Molecular docking analysis of phytocompounds from Psoralea corylifolia seeds against the protein of crystal structure of beta toxin from Staphylococcus aureus F277A, P278A mutant with bound calcium ions (PDB ID: 3I46). The interaction of protein and ligand reveals docking scores in all ligands. The highest docking scores reveals by Psoralidin, Corylidin, Bavachin, Neobavaisoflavone, Corylinal and Corylifol A. The present study reveals that Psoralea corylifolia seeds are acting as alternate medicine for treating beta toxin and various skin infections.
KEYWORDS: *Cow urine, Psoralea corylifolia seeds, docking, S. aureus*

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INTRODUCTION

The medicinal herb *Psoralea corylifolia* L. is on the verge of extinction. It is widely distributed in India, China, and Pakistan's Himalayan regions [1, 2]. And the *Psoralea* genus is native to North America [3]. Because of its ability to cure leprosy, *P. corylifolia* is also known as 'Kusthanashini,' or leprosy killer. It has a wide range of applications since it is an integral component of both the allopathic and conventional medical systems in different parts of the world. Psoriasis, leucoderma, and vitiligo are all treated with it in traditional Chinese medicine and Indian systems of medicine such as Ayurveda, Siddha, and Unani [4].

The plant is assumed to be warm in Chinese medicine, so it is used to treat kidney and spleen problems. Regardless, the plant's seeds are used as a diuretic, laxative, anti-parasitic, aphrodisiac, and competing remedy. Psoriasis, eczema, leukoderma, alopecia, and inflammation have all been treated with the seed paste [5, 6].

Even though seeds contain the majority of bioactive compounds of medicinal interest, *Psoralea corylifolia* seeds have been the subject of research. Psoralen, Isopsoralen, Bakuchiol, Bakuchicin, Bavachin, Isobavachin, Bavachinin, Bavachlcone, Isobavachalcone, Neobavachalcone, Corylifol A, B, C, D, E, Corylifolin, Corylifolinin, and other bioactive compounds exist [5, 7].

Bakuchi seed powder is mixed with cow's urine and Haratala Bhasma (yellow arsenic) in a 4:1 ratio for leucoderma. Leucoderma lesions are treated with this paste. External application of bakuchi seed powder combined with buttermilk is used to treat scabies and ringworm infestations [8, 9, & 10]. Bakuchi was combined with other herbs such as *Phyllanthus emblica* Linn. and *Acacia catechu* in a polyherbal extracts decoction that was recommended for treating leucoderma. As stated earlier, the seeds of *Psoralea corylifolia* have long been used as a medicinal agent in both Chinese and Ayurvedic medicine systems. Some of its biological activities have been recorded as antibacterial [11, 12], antiviral [13], antifungal [14, 15], anticancer and apoptotic [16], protective [17, 18, & 19].

Staphylococcus aureus is a highly important bacterium that causes infections in people all over the world. In healthy people, it causes a 30% infection rate. Despite the fact that it is asymptomatic, it can be lethal in immune-compromised patients. *Staphylococcus aureus* produces numerous cell surfaces and secreted virulence factors that allow it to cause a wide range of human illnesses, from mild boils to fatal toxic shock syndrome and necrotizing pneumonia. Certain strains of *Staphylococcus aureus* contain beta toxins [20, 21]. In humans, Staphylococcus aureus infections usually start with colonization of the mucus membrane or the skin. It produces toxins and cytolysins (leukocidins) that affect RBCs, epithelial cells in large numbers, and the immune system. Cytolysins include alpha, beta, gamma, and delta toxins. Exotoxins are beta poisons, and sphingomyelinase is a neutral enzyme [22].

The goal of this study was to identify the bioactive compounds in cow urine extracts of *Psoralea corylifolia* seeds, as well as to conduct a molecular docking review of the phytocompounds discovered in order to investigate molecular interactions.

MATERIAL AND METHODS

COLLECTION AND PROCESSING OF SEEDS SAMPLES:

The seed of *Psoralea corylifolia* was collected in the local folk medicine market in Cuddalore District, Tamil Nadu. After the collection of seeds, it was ground coarsely by using Morter and Pestle. The ground seed samples are sieved and stored for further processes.

PREPARATION OF EXTRACT:

10g of seeds powder of *Psoralea corylifolia* was mixed with 100 ml of fresh cow urine and incubated for 3 days. After incubation, the extract was filtered through Whatman No.1 filter paper. The filtered extract was used for further analysis.

LC-MS ANALYSIS:

The quantitative phytochemical analysis of cow urine extracts of *Psoralea corylifolia* seeds by the hyphenated technique of Liquid Chromatography-Mass spectrometry analysis. Result analysis of compounds by peak value.

IDENTIFICATION OF PHYTOCONSTITUENTS:

The spectrum of LC-MS analysis unknown components were compared with the spectrum of the known components stored in Wiley9 library and PubChem databases.

PASS PREDICTION:

PASS prediction is an online tool to predict the biological activity of compounds. PASS prediction analysis of these bioactive compounds obtained from LC-MS analysis. By using PASS prediction online tool (http://www.way2drug.com/PASSOnline/), Anti-bacterial activity of cow urine extracts of *Psoralea corylifolia* seeds.

MOLECULAR DOCKING ANALYSIS:

DOCKING ANALYSIS:

The molecular docking study aimed to determine the most derived target protein-ligand complex structure. The AutoDock Vina protocol with BIOVIA Discovery studio visualization was used to determining the active binding modes between the ligands and the target proteins. The parameters of the attributes are defining by the run ligand-receptor site. The algorithm uses protein–ligand interaction energy, Hydrogen bonds; binding energies were used to quantify the affinity of ligand binding. The docking energy is stated in Negative values. Higher negative energy values indicated the higher binding affinity of protein and ligand.

RETRIEVAL OF TARGET PROTEIN:

The protein of crystal structure of beta toxin from *Staphylococcus aureus* F277A, P278A mutant with bound calcium ions of 3i46 was obtained from RCSB Protein Data Bank. And the UNIPROT ID of 3i46 was A7LAI8 (http://chlorine.atomistry.com/pdb3i46.html).

LIGAND GENERATION:

For ligand generation, LC-MS analysis of Cow urine extracts of *Psoralea corylifolia* seeds compounds was used for molecular docking. The database of obtained compounds from Pubchem and the 3D structures of identified compounds were downloaded in SDF file format. Then that file was converted into a PDB file for further analysis by using Open Babel software. The compounds are used for the prediction of ligand properties such as pH, Molecular weight, Hydrogen bonds, acceptors, logP values and Refractive index. These compounds were screened for drug – likeliness according to Lipinski's rule of five. The drug – likeliness of Lipinski's rule of five was predicted by using online (scfbio-iitd.res.in).

RESULTS

The phytoconstituents present in cow urine with *Psoralea corylifolia* seeds were analyzed through Liquid Chromatography-Mass Spectrometry (LC-MS). Results obtained from the LC-MS analysis and names of the compounds, molecular formula, logP value, Hydrogen bond donor count, Hydrogen bond acceptor count were retrieved from PubChem databases are in Table 1 and Graphical presentation in Fig 3.

PASS Prediction:

All the compounds are predicted biological activity through the PASS prediction online tool. And it is observed that the Antibacterial activity of *Staphylococcus aureus* and other various microorganisms.

Molecular Docking analysis:

For docking analysis with 18 compounds retrieved from Pubchem databases and Standard drugs such as Methicillin and Cefazolin. All these 20 compounds are docked with the 3I46 protein retrieved from the RCSB PDB databank. The docking studies of Beta toxin of Staphylococcus aureus (3I46) of binding active site were analyzed by using the CASTp online server. After identification of protein active binding site, molecular docking was analyzed by using Autodock vina MGL tools. In Autodock vina protein is loaded with macromolecules, and waters are removed. Then hydrogen polar bonds are added manually and add charges. Then macromolecule files are saved as PDBQT. Ligand files are input and saved as PDBQT files. Grid box are formed in centre grid are X = 4.139, Y = 6.845 and Z = -5.199. And size X = 20, Y = 20 and Z = 20. Then configuration file was made by using all the details correctly. Command prompts are run by using data. After the file was generated, it was split by using Vina split. Then it is analyzed by using BIOVIA Discovery studio software used for protein and ligand interactions and publication-quality images [23]. After protein and ligand docking analysis, interactions of protein-ligand sites (amino acid), the phytocompounds of cow urine extracts of *Psoralea corylifolia* seeds against crystal structure of Beta toxin of *Staphylococcus aureus* F277A, P278A mutant with bound Calcium ions (3I46) shows the binding activity of all the ligand. In this analysis of ligand interactions with *Staphylococcus aureus* having the highest interactions are shown in Table 2 and Fig 4.

Fig 1: (a) Structure of 3I46 - crystal structure of beta toxin from *Staphylococcus aureus* F277A, P278A mutant with bound calcium ions. (b) CASTp – 3I46 active site.

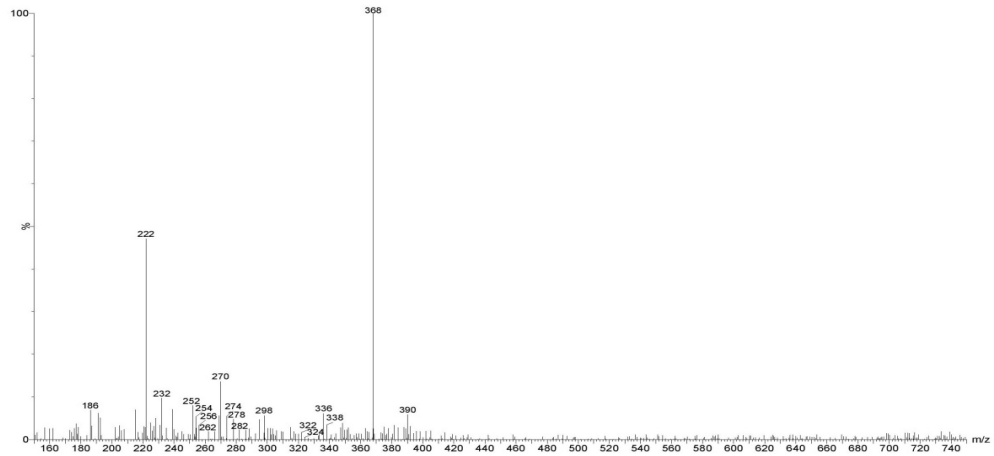

Fig 2: LC-MS analysis of Cow Urine extracts of *Psoralea corylifolia* seeds

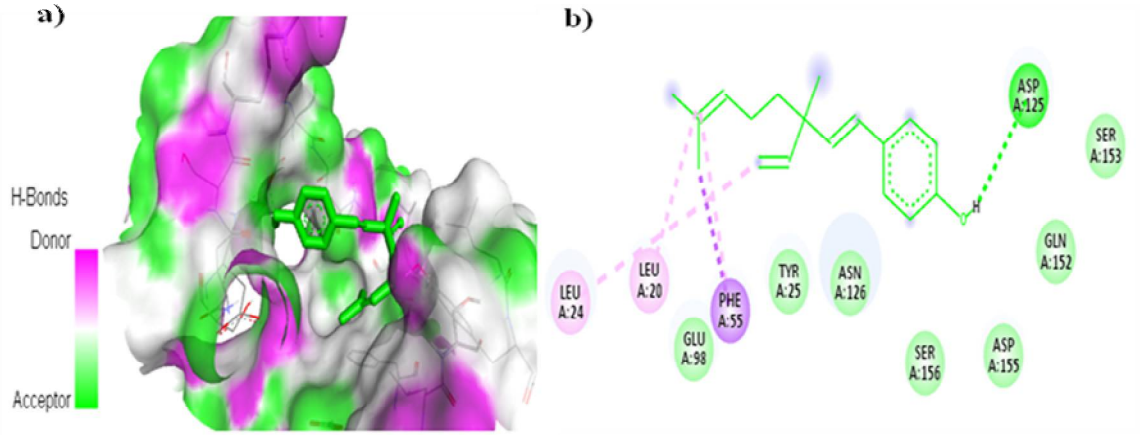

Fig 3: a) Ligand Interaction and b) 2D binding interaction of Bakuchiol derivatives with active site of 3I46 receptor.

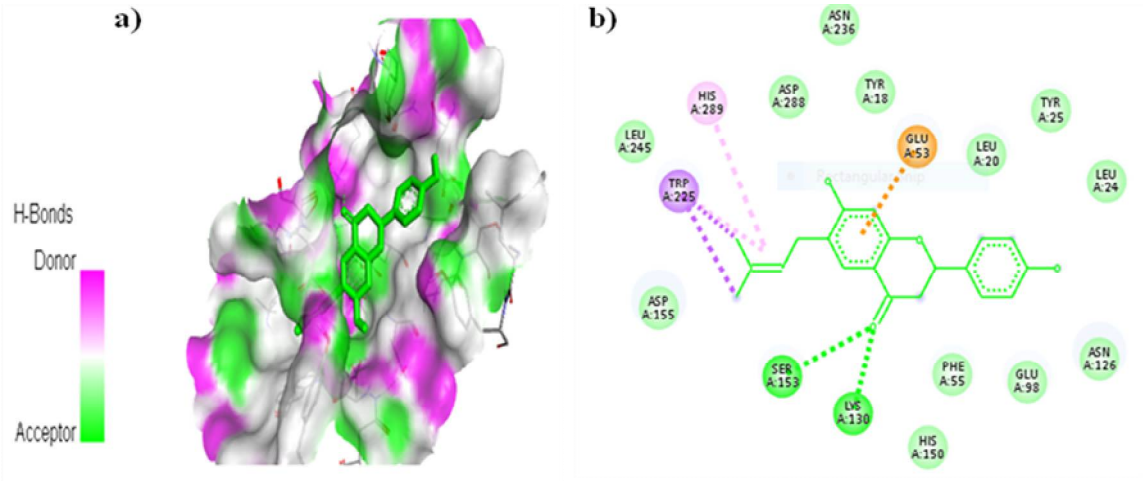

Fig 4: a) Ligand Interaction and b) 2D binding interaction of Bavachin derivatives with active site of 3I46 receptor.

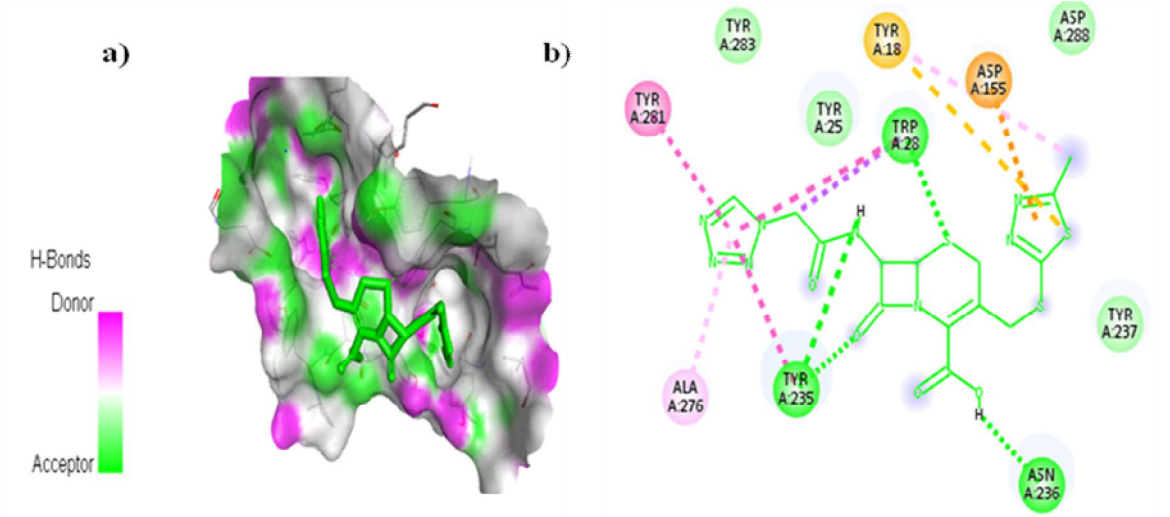

Fig 5: a) Ligand Interaction and b) 2D binding interaction of Cefazolin derivatives with active site of 3I46 receptor.

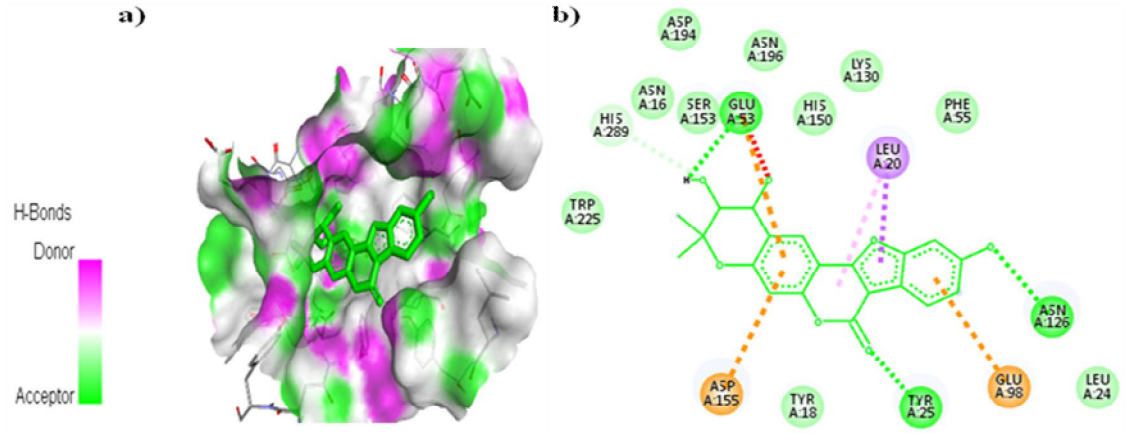

Fig 6: a) Ligand Interaction and b) 2D binding interaction of Corylidin derivatives with active site of 3I46 receptor.

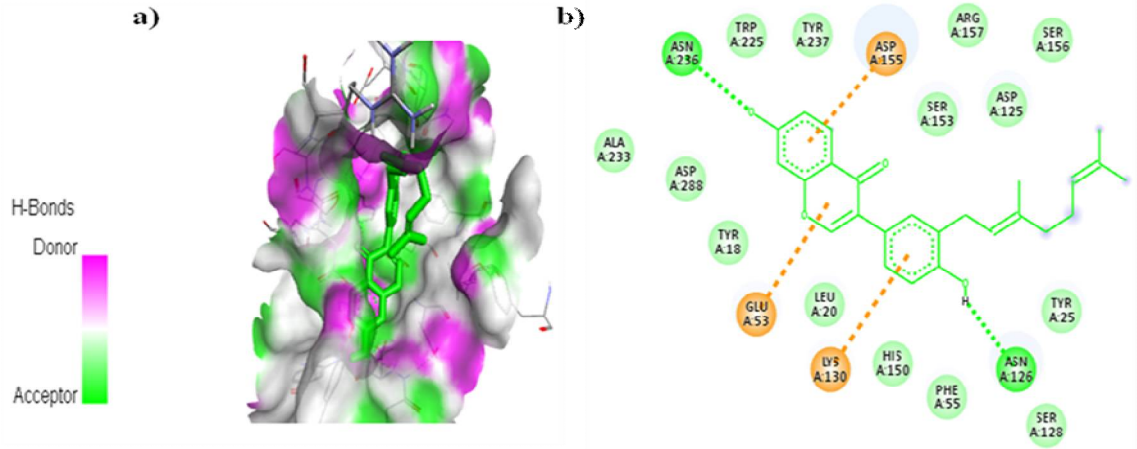

Fig 7: a) Ligand Interaction and b) 2D binding interaction of Corylifol A derivatives with active site of 3I46 receptor.

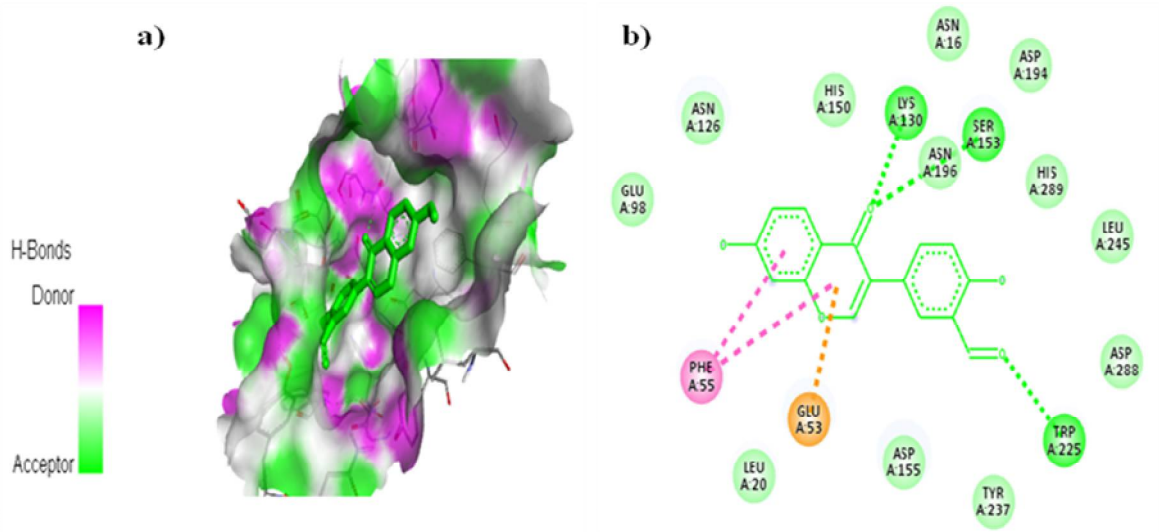

Fig 8: a) Ligand Interaction and b) 2D binding interaction of Corylinal A derivatives with active site of 3I46 receptor.

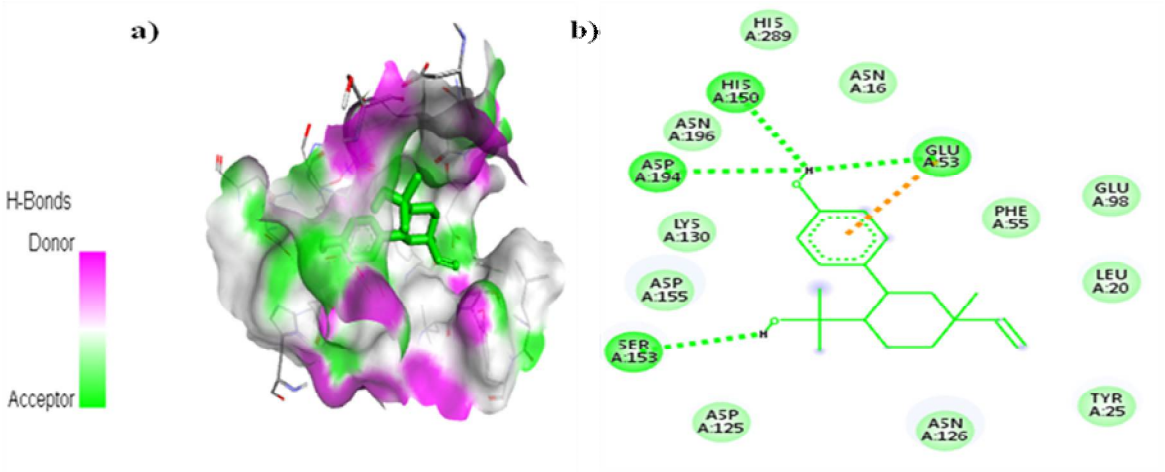

Fig 9: a) Ligand Interaction and b) 2D binding interaction of Cyclobakuchiol – C derivatives with active site of 3I46 receptor.

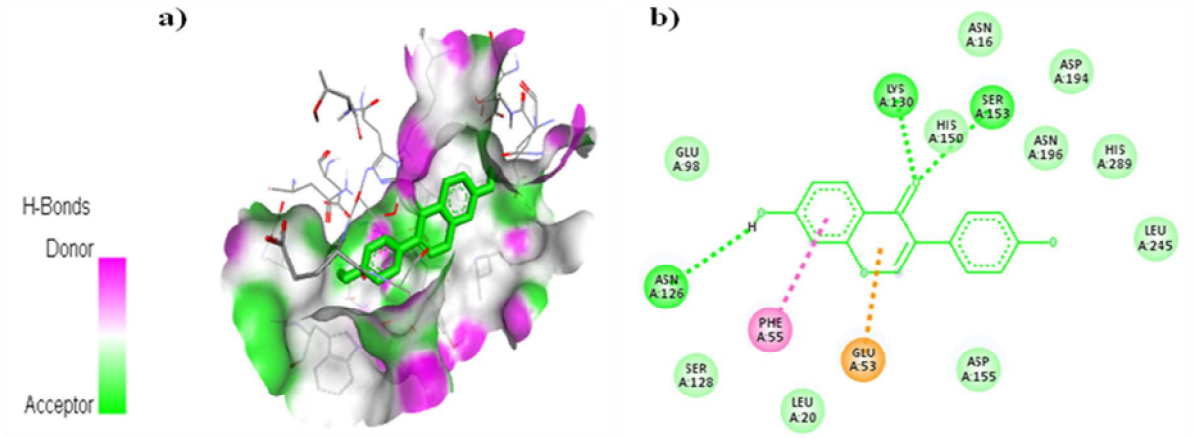

Fig 10: a) Ligand Interaction and b) 2D binding interaction of Daidzein derivatives with active site of 3I46 receptor.

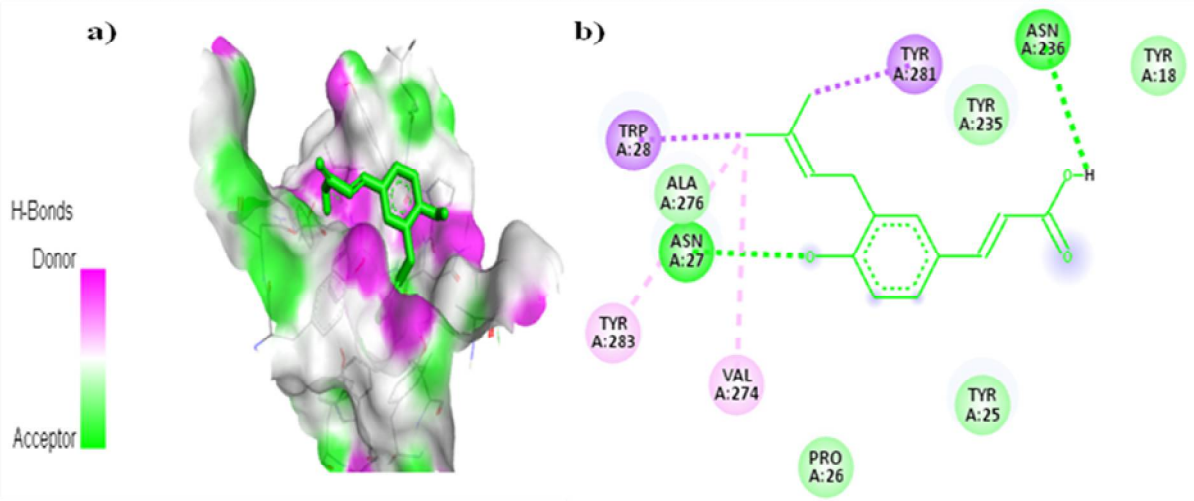

Fig 11: a) Ligand Interaction and b) 2D binding interaction of Drupanin derivatives with active site of 3I46 receptor.

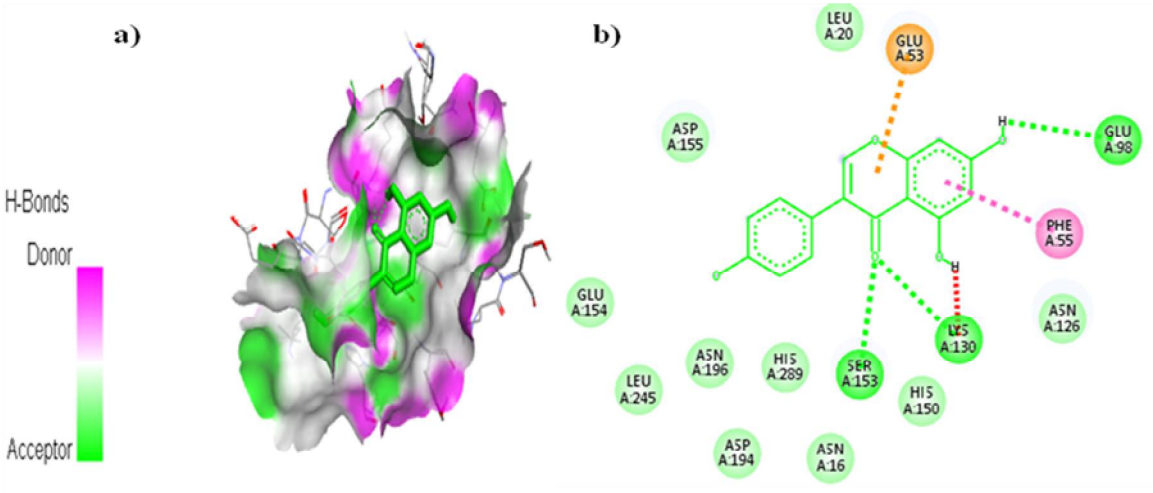

Fig 12: a) Ligand Interaction and b) 2D binding interaction of Genistein derivatives with active site of 3I46 receptor.

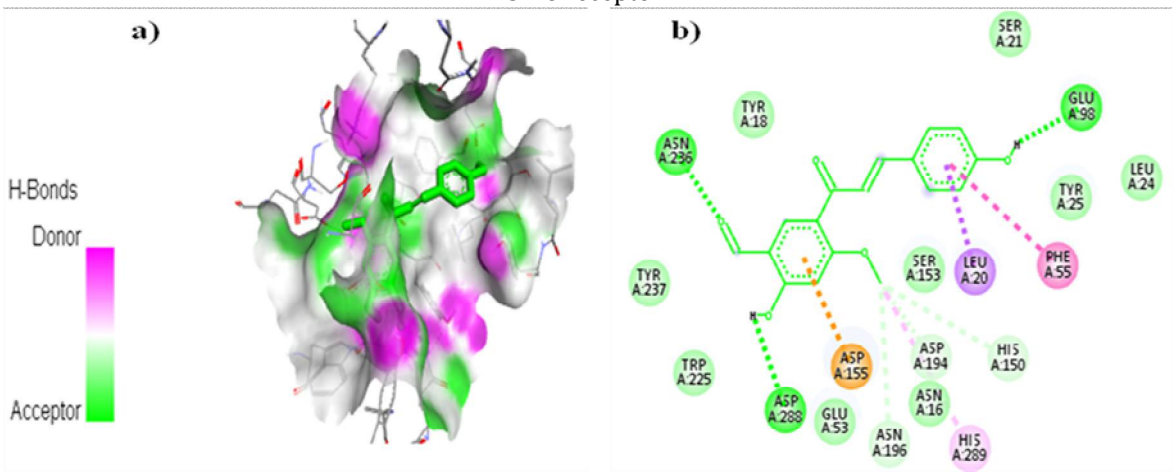

Fig 13: a) Ligand Interaction and b) 2D binding interaction of Isoneobavachalcone derivatives with active site of 3I46 receptor.

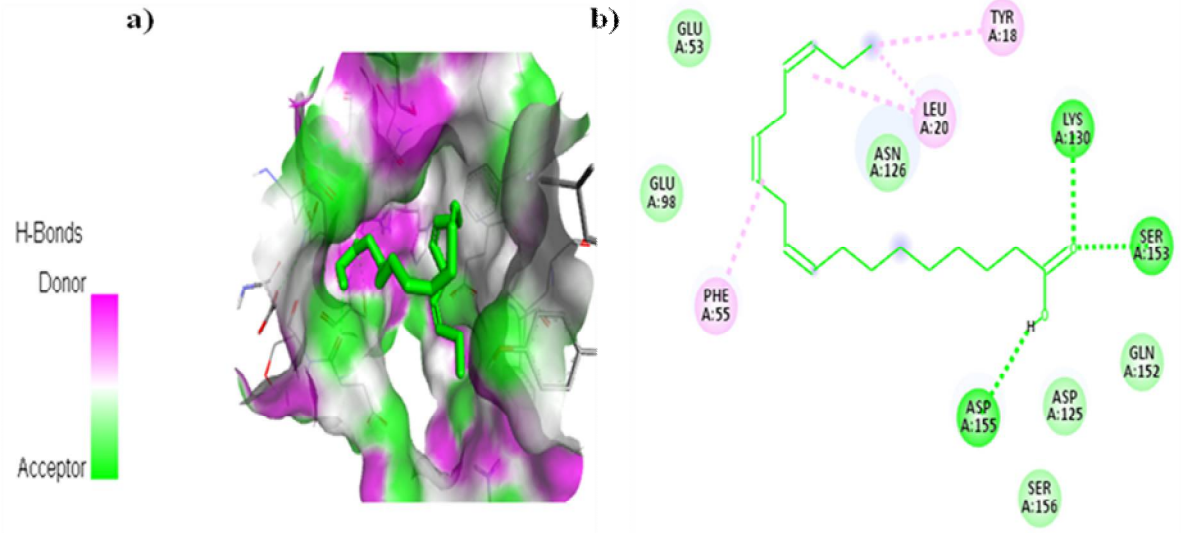

Fig 14: a) Ligand Interaction and b) 2D binding interaction of Linolenic acid derivatives with active site of 3I46 receptor.

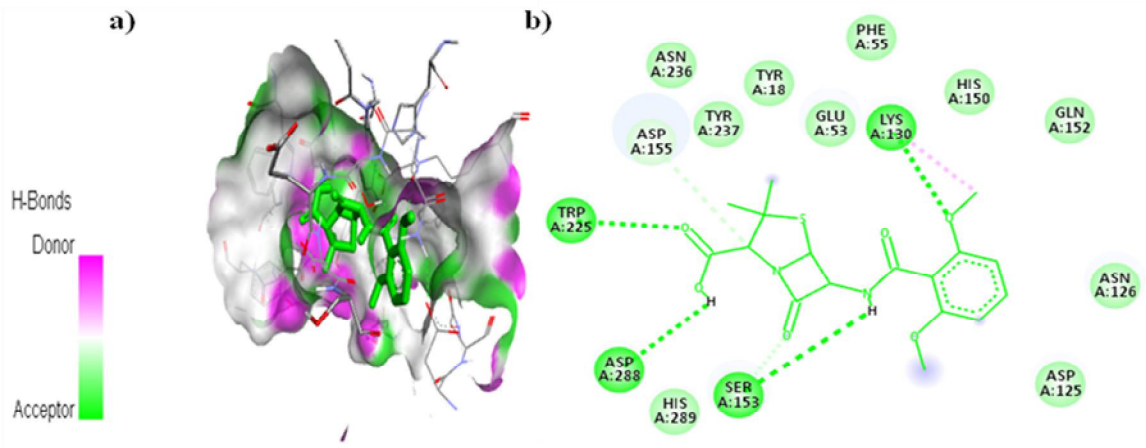

Fig 15: a) Ligand Interaction and b) 2D binding interaction of Methicillin derivatives with active site of 3I46 receptor.

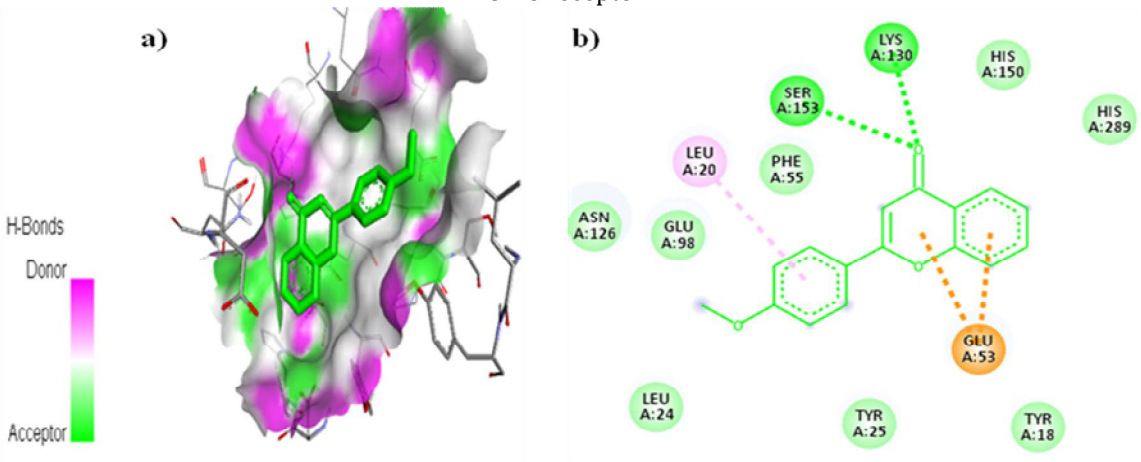

Fig 16: a) Ligand Interaction and b) 2D binding interaction of Methoxyflavone derivatives with active site of 3I46 receptor.

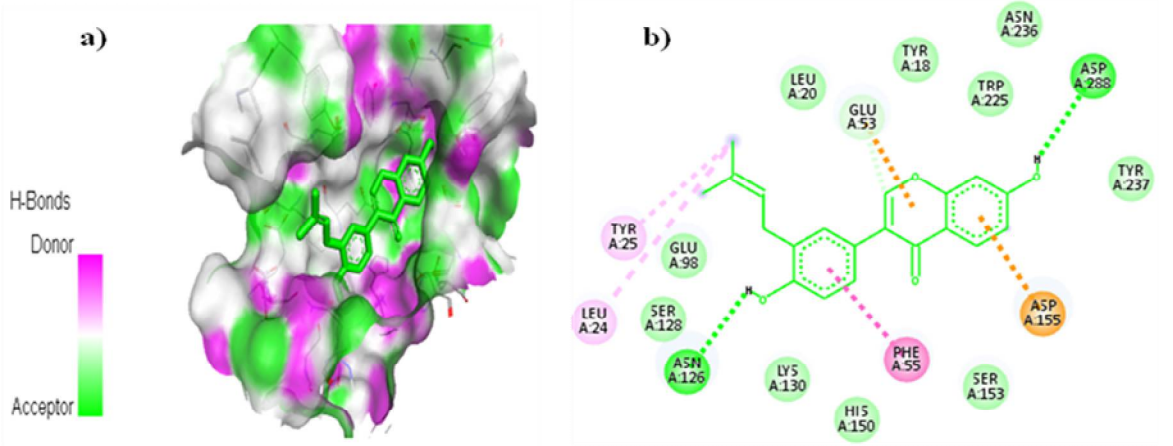

Fig 17: a) Ligand Interaction and b) 2D binding interaction of Neobavaisoflavone derivatives with active site of 3I46 receptor.

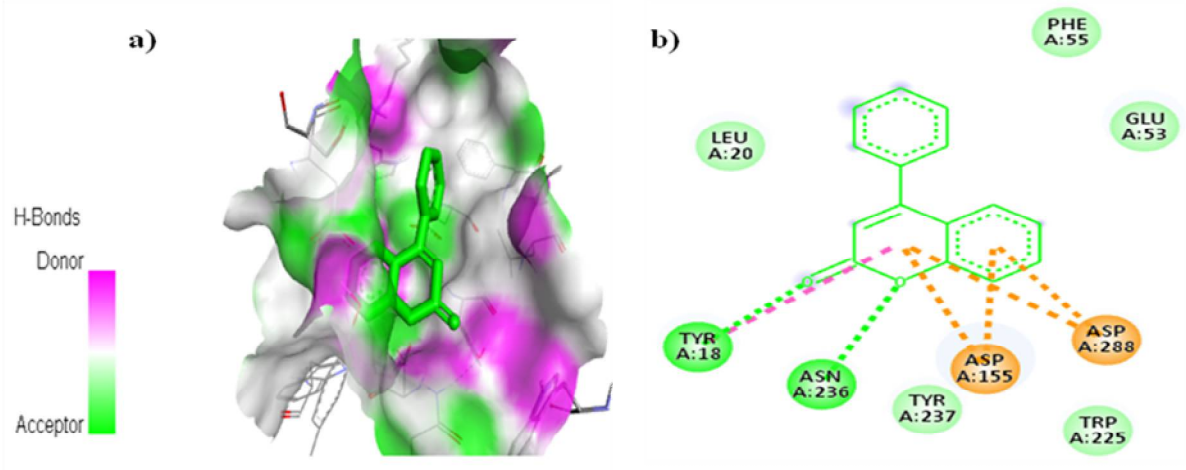

Fig 18: a) Ligand Interaction and b) 2D binding interaction of Phenylcoumarin derivatives with active site of 3I46 receptor.

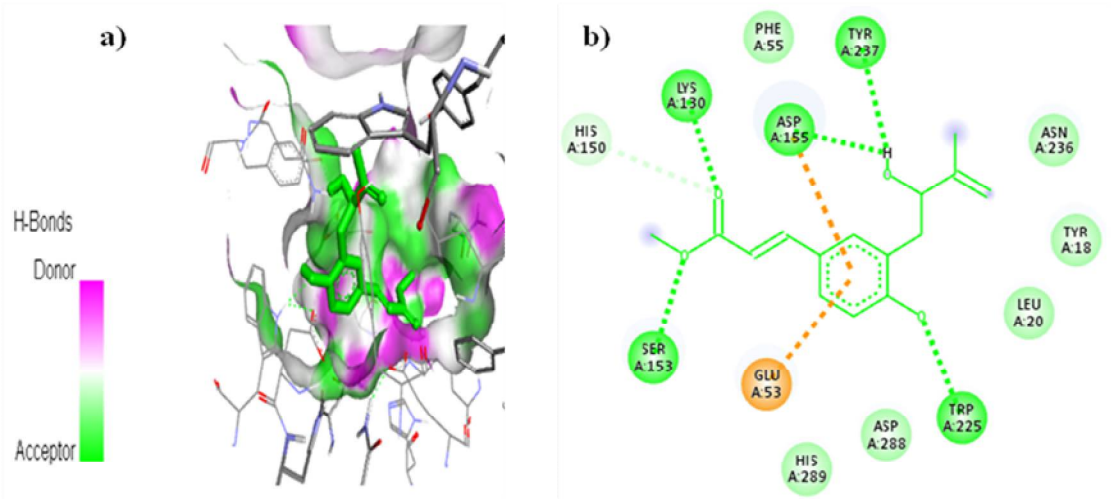

Fig 19: a) Ligand Interaction and b) 2D binding interaction of Plicatin-A derivatives with active site of 3I46 receptor.

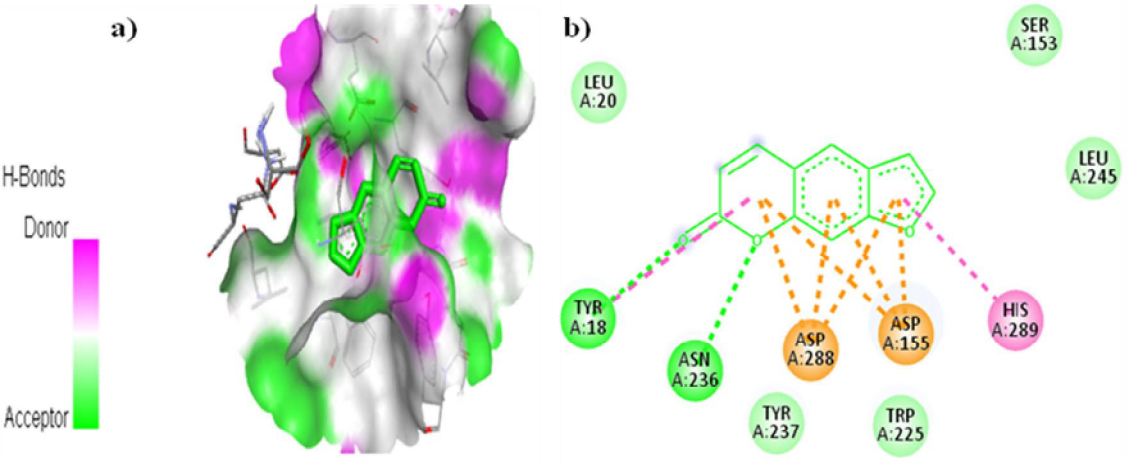

Fig 20: a) Ligand Interaction and b) 2D binding interaction of Psoralen derivatives with active site of 3I46 receptor.

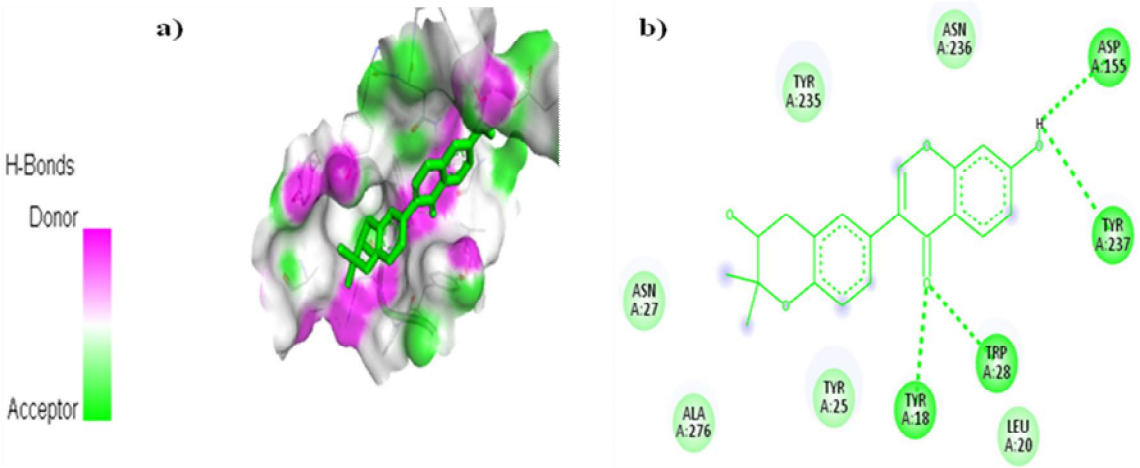

Fig 21: a) Ligand Interaction and b) 2D binding interaction of Psoralenol derivatives with active site of 3I46 receptor.

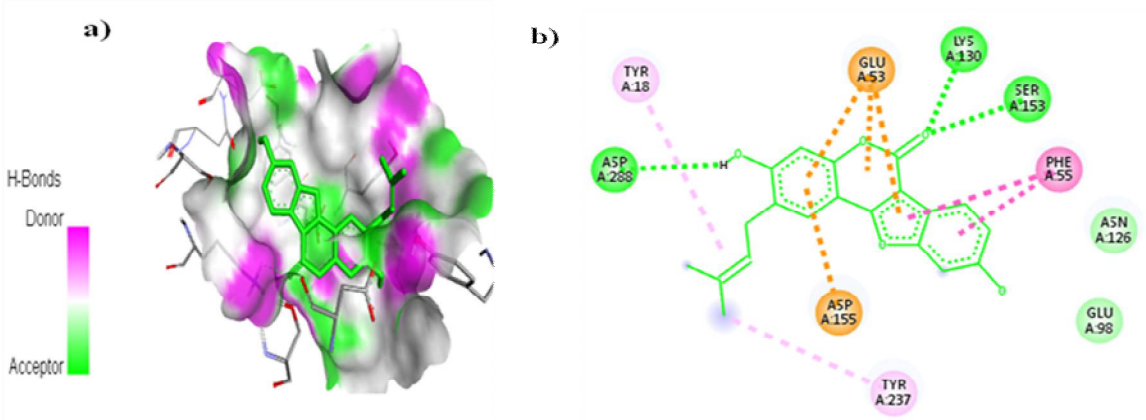

Fig 22: a) Ligand Interaction and b) 2D binding interaction of Psoralidin derivatives with active site of 3I46 receptor.

Table 1: Results of Compounds from LC-MS analysis

S.No	Compounds Names	PubChem CID	Molecular formula	Molecular Weight (g/mol)	HBD	HBA	logP
1.	Corylidin	5316096	$C_{20}H_{16}O_7$	368.3	3	7	2
2.	C-Phenylcoumarin	613729	$C_{15}H_{10}O_2$	222.24	0	2	3.1
3.	Psoralen	6199	$C_{11}H_6O_3$	186.16	0	3	2.3
4.	Drupanin	6440361	$C_{14}H_{16}O_3$	232.27	2	3	3.4
5.	Methoxyflavone	71793	$C_{16}H_{12}O_3$	252.26	0	3	3.5
6.	Daidzein	5281708	$C_{15}H_{10}O_4$	24.24	2	4	2.5
7.	Bakuchiol	5468522	$C_{18}H_{24}O$	256.18	1	1	6.1
8.	Plicatin - A	15730631	$C_{15}H_{18}O_4$	262.3	2	4	2.7
9.	Genistein	5280961	$C_{15}H_{10}O_5$	270.24	3	5	2.7
10.	Cyclobakuchiol - C	101956380	$C_{18}H_{26}O_2$	274.4	2	2	4.5
11.	Linolenic acid	5280934	$C_{18}H_{30}O_2$	278.4	1	2	5.9
12.	Corylinal	44257227	$C_{18}H_{30}O_2$	282.25	2	5	2.5
13.	Isoneobavachalcone	5318608	$C_{17}H_{14}O_5$	298.29	2	5	3
14.	Neobavachalcone	5320053	$C_{20}H_{18}O_4$	322.4	2	4	4.4
15.	Bavachin	14236566	$C_{20}H_{20}O_4$	324.4	2	4	4.1
16.	Psoralidin	5281806	$C_{20}H_{16}O_5$	336.3	2	5	4.7
17.	Psoralenol	5320772	$C_{20}H_{18}O_5$	338.4	2	5	2.8
18.	Corylifol - A	25056407	$C_{25}H_{26}O_4$	390.5	2	4	6.3

Table 2: Molecular Docking Analysis

Ligand	Docking Score (kcal/mol)	Interacting Residues	Distance (Å)	Category	Type
Bakuchiol	-5.5	ASP125 PHE55 LEU20 LEU24 PHE55	2.37 3.89 4.90 5.14 4.75	Hydrogen Bond Hydrophobic Hydrophobic Hydrophobic Hydrophobic	Conventional Pi-Sigma Alkyl Alkyl Pi-Alkyl
Bavachin	-8.2	LYS130 GLU53 ASP155 ASP288 PHE55 HIS289 LEU20 TYR25	2.32 3.27 4.51 4.76 5.69 5.12 4.65 5.42	Hydrogen Bond Hydrogen Bond Electrostatic Electrostatic Hydrophobic Hydrophobic Hydrophobic Hydrophobic	Conventional Carbon Pi-Anion Pi-Anion Pi-Pi Stacked Pi-Pi T shaped Alkyl Pi-Alkyl
Cefazolin	-6.6	TRP28 TYR235 TYR235 ASN236 ASP155 TRP28 TYR18 TYR281 ALA276	2.35 2.72 3.05 2.98 4.15 3.85 5.93 4.55 4.71	Hydrogen Bond Hydrogen Bond Hydrogen Bond Hydrogen Bond Electrostatic Hydrophobic Other Hydrophobic Hydrophobic	Conventional Conventional Conventional Conventional Pi-Anion Pi-Sigma Pi-Sulfur Pi-Pi T-shaped Pi-Alkyl
Corylidin	-8.3	TYR25 ASN126 GLU53 HIS289 GLU98 ASP155 LEU20	2.19 2.37 2.04 2.94 4.52 4.81 3.94	Hydrogen Bond Hydrogen Bond Hydrogen Bond Electrostatic Electrostatic Electrostatic Hydrophobic	Conventional Conventional Conventional Carbon Pi-Anion Pi-Anion Pi-Sigma
CorlifolA	-7.2	ASN236 ASN126 LYS130 GLU53 ASP155	2.26 2.12 4.52 4.30 3.84	Hydrogen Bond Hydrogen Bond Electrostatic Electrostatic Electrostatic	Conventional Conventional Pi-Cation Pi-Anion Pi-Anion
Corylinal	-7.3	LYS130 SER153 TRP225 GLU53 PHE55	2.26 2.85 2.79 3.64 5.94	Hydrogen Bond Hydrogen Bond Hydrogen Bond Electrostatic	Conventional Conventional Conventional Pi-Anion Pi-Pi Stacked

				Hydrophobic	
Cyclobakuchiol C	-5.7	SER153 GLU53 HIS150 ASP194	2.67 2.97 2.71 3.08	Hydrogen Bond Hydrogen Bond Hydrogen Bond	Conventional Conventional Conventional Conventional
Daidzein	-7.1	LYS130 SER153 ASN126 GLU53 PHE55	2.05 2.68 2.84 3.71 4.69	Hydrogen Bond Hydrogen Bond Hydrogen Bond Electrostatic Hydrophobic	Conventional Conventional Conventional Pi-Anion Pi-Pi Stacked
Drupanin	-6.0	ASN27 ASN236 TRP28 TYR281 VAL274 TYR283	2.64 2.67 3.76 3.63 5.08 4.66	Hydrogen Bond Hydrogen Bond Hydrophobic Hydrophobic Hydrophobic Hydrophobic	Conventional Conventional Pi-Sigma Pi-Sigma Alkyl Pi-Alkyl
Genistein	-7.0	LYS130 SER153 GLU98 GLU53 PHE55	2.36 2.73 2.93 3.64 4.70	Hydrogen Bond Hydrogen Bond Hydrogen Bond Electrostatic Hydrophobic	Conventional Conventional Conventional Pi-Anion Pi-Pi Stacked
Isoneobavachalcone	-6.3	ASN236 GLU98 ASP288 HIS150 ASP194 ASN196 ASP155 LEU20 PHE55 HIS289	2.09 1.79 2.16 3.55 3.46 3.61 4.14 3.66 5.56 5.28	Hydrogen Bond Hydrogen Bond Hydrogen Bond Hydrogen Bond Hydrogen Bond Electrostatic Hydrophobic Hydrophobic Hydrophobic	Conventional Conventional Conventional Carbon Carbon Carbon Pi-Anion Pi-Sigma Pi-Pi Stacked Pi-Alkyl
Linolenic Acid	-4.5	LYS130 SER153 ASP155 LEU20 TYR18 PHE55	2.42 2.01 2.32 5.28 5.26 4.21	Hydrogen Bond Hydrogen Bond Hydrogen Bond Hydrophobic	Conventional Conventional Conventional Alkyl Alkyl Pi-Alkyl

				Hydrophobic Hydrophobic	
Methicillin	-6.5	LYS130 TRP225 SER153 ASP288 SER153 ASP155 LYS130	2.41 2.67 3.03 2.77 3.18 3.44 5.36	Hydrogen Bond Hydrogen Bond Hydrogen Bond Hydrogen Bond Hydrogen Bond Hydrophobic	Conventional Conventional Conventional Conventional Carbon Carbon Alkyl
Methoxyflavone	-6.4	LYS130 SER153 GLU53 LEU20	2.25 2.65 3.90 5.34	Hydrogen Bond Hydrogen Bond Electrostatic Hydrophobic	Conventional Conventional Pi-Anion Pi-Alkyl
Neobavaisoflavone	-8.0	ASN126 ASP288 GLU53 ASP155 PHE55 LEU24 TYR25	2.64 2.66 3.33 4.07 4.52 5.18 5.07	Hydrogen Bond Hydrogen Bond Hydrogen Bond Electrostatic Hydrophobic Hydrophobic Hydrophobic	Conventional Conventional Carbon Pi-Anion Pi-Pi Stacked Alkyl Pi-Alkyl
Phenylcoumarin	-6.7	TYR18 ASN236 ASP155 ASP288	2.61 2.52 4.09 4.56	Hydrogen Bond Hydrogen Bond Electrostatic Electrostatic	Conventional Conventional Pi-Anion Pi-Anion
PlicatinA	-5.7	LYS130 SER153 TYP225 ASP155 TYR237 HIS150 GLU53	2.08 2.63 2.34 2.70 2.46 3.61 4.80	Hydrogen Bond Hydrogen Bond Hydrogen Bond Hydrogen Bond Hydrogen Bond Hydrogen Bond Electrostatic	Conventional Conventional Conventional Conventional Conventional Carbon Pi-Anion
Psoralidin	-8.4	LYS130 SER153 ASP288 GLU53 ASP155 PHE55	2.54 2.86 2.76 3.90 4.53 4.55	Hydrogen Bond Hydrogen Bond Hydrogen Bond	Conventional Conventional Carbon Pi-Anion Pi-Anion Pi-Pi Stacked

		TYR18 TYR237	5.33 4.96	Electrostatic Electrostatic Hydrophobic Hydrophobic Hydrophobic	Pi-Alkyl Pi-Alkyl
Psoralen	-6.2	TYR18 ASN236 ASP155 ASP288 HIS289	2.84 2.59 4.43 4.58 5.14	Hydrogen Bond Hydrogen Bond Electrostatic Electrostatic Hydrophobic	Conventional Conventional Pi-Anion Pi-Anion Pi-Pi T-shaped
Psoralenol	-6.6	TYR18 TYR28 ASP155 TYR237	2.26 2.09 2.09 2.88	Hydrogen Bond Hydrogen Bond Hydrogen Bond Hydrogen Bond	Conventional Conventional Conventional Conventional

DISCUSSION

The physicochemical properties of all phytocompounds were analyzed by using Lipinski's rule of drug-likeness. The crystal structure of beta toxin from *Staphylococcus aureus* F277A, P278A mutant with bound calcium ions (3I46) and the ligand of all phytoconstituents were analyzed by docking and the protein-ligand interactions are revealed the highest binding activities. Analysis docking ligands against *Staphylococcus aureus* shows highest docking scores are Psoralidin (-8.4 kcal/mol), Corylidin (-8.3 kcal/mol), Bavachin (-8.2 kcal/mol), Neobavaisoflavone (-8.0 kcal/mol), Corylinal (-7.3 kcal/mol) and Corylifol A (-7.2 kcal/mol). Docking scores are better than standard antibiotics. It shows the interaction of protein-ligand with various categories such as hydrogen bonds, electrostatic, hydrophobic and types as conventional, Pi – Alkyl, Alkyl, Pi – Anion, Sulfur, Pi – Pi stacked. Docking studies of protein and ligand show amino acid residues such as LYS 130, ASP 155, ASP 288, SER 153, TYR 18, TYR 237 and GLU 53. The outcome was determined that the phytoconstituents of cow urine extracts of *Psoralea corylifolia* seeds can be used as an alternative medicine for various skin infections.

CONCLUSION

Psoralea corylifolia seeds are used for many biological activities such as Anti-bacterial, Anti-fungal, Anti-psoriatic, etc. Seeds are mixed with cow urine and ground as paste and used for leucoderma in the ancient period of India. The present docking studies concluded that the phytocompounds present in the seeds of *Psoralea corylifolia* having great effects to treat *Staphylococcus aureus* infections. Further studies will be carried out for analyzing various biological activities.

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CONFLICT OF INTEREST

There is no conflict of interest.

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