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In-Silico STUDIES, CHARACTERIZATION, ADMET PREDICTION, AND MOLECULAR DOCKING OF VIGNA VEXILLATA CONSTITUENTS AND THEIR CNS STIMULANT ACTIVITY

[1]Vaibhav N. Mohare*, [2]Alpana J. Asnani, [3]Swapnja B. Gunjarkar, [4]Samiksha R. Mehare, [5]Monika W. Parate

[1]Department of Pharmaceutical Chemistry, Priyadarshini J. L. College of Pharmacy, Nagpur, Maharashtra, India – 440016

Corresponding Author's:-
Vaibhav N. Mohare
Priyadarshini J. L. College of Pharmacy, Nagpur

ABSTRACT:-
There have been several studies about the bioactivities of the seeds from the *Vigna* genus, which are significant food sources. The entire *V. vexillata* plant, including the flowers and pods, was air-dried and pulverized. Methanol was then extracted under reflux and concentrated to create a dark brown syrup. The binding affinity and interactions with amino acids of phytochemicals were evaluated. Target protein protein homology modeling, protein structure validation, and energy minimization were all completed. A comparative *in-silico* docking analysis with the standard drug was conducted using phytochemicals that had been mentioned in the literature as having properties related to CNS stimulant activities. These phytochemicals were studied for their absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties and those that passed ADMET filters. Using AutoDock Vina, a preliminary docking study was performed, then AutoDock 4.2.6 and SwissDock were used to validate the results.

Keywords: *Vigna*; Isoflavone, Molecular Docking, PyRx Vina auto dock, Chemsketch, ADMET Prediction.

Introduction

An evergreen climber or trailing plant in the *Vigna* genus is *V. vexillata* (L.) A. Rich (Fabeaceae). Tropical Africa, India, Indochina, Australia, Japan, Korea, China, and Taiwan are among the regions where this species is extensively found. In Taiwan, the *Vigna vexillata* is an edible monsoon perennial leguminous specieswith fusiform roots occurs in the hills of Western Ghats. On two- to four-flowered, 7.5-30 cm (3.0-11.8 in) long peduncles with a protruding keel that forms an uncurved beak, the blooms are 2.5 cm (0.98 in) long and pink, purple, or yellow. At elevations between 1000 and 1800 m high in the central highland region of Taiwan, the *Vigna* genus often thrives in grassland with marginal shrub. The main chemical

constituents are present in plant such as quercetin, abscisic acid, daidzein, daidzin, isovitexin, vitexin, blumenol, dihydrophaseic acid, vanillic acid. The plant contains alkaloids, sugar & carbohydrates, flavonoids, tannins & steroids, proteins & amino acid. *Vigna vexillata* is use in Ayurvedic system of medicine for joint disorders, arthritis, swellings in joint. The leaves has been used in hypoglycemic, Antihypertensive, Cholesterol reduction, Antioxidants, Antibacterial, anti-cancer bioactivities.[1]

Chemical constituent of *Vigna vexillata:*

The entire *V. vexillata* plant, including the flowers and pods, was air-dried and pulverized. Methanol was then extracted under reflux and concentrated to create a dark brown syrup. The methanol extracts were suspended in water and subsequently fractionated with chloroform to produce chloroform and water soluble, respectively. One novel sterol and two new isoflavones were identified with the use of a mixture of traditional chromatographic methods, 1D and 2D NMR elucidations, and mass spectrum studies. 37 more known compounds are also present, such as stigmast-4-en-3-one and stigmast-4,22-dien-3-one. [4], (27RS) the 27-diol cycloart-28-en-6[5], β-sitosterol, and stigmasterol[26] [8] [9],sitosterol cis-p coumarate sitosterol trans-p coumarate lupeol and [5], (6-hydroxy-sitosterone; [6] , Sitosterol ferulate [27][7] ,(20R)-22E cholest-4-ene-3,6-dione[9], methylparaben, p-hydroxybenzoic acid,[2],[3], and [17] p-hydroxybenzaldehyde, vanillic acid [10], genistein[11] , dehydrovomifoliol[12] , β-sitostenone [13] , 5,7,4'-trihydroxy-3'-methoxy isoflavone[14] , daidzein [14] , indole-3-carboxaldehyd [15], and abscisic acid [16], Trans-cinnamic acid [16], -sitosteryl-3-O-glucopyranoside [17], trans-methyl p-coumarate [18], salicylic acid [19], tachioside [20], and 3-hydroxy--damascone[21], p-hydroxyl phenethanol[22], trans p-coumaric acid [23], 3,6-dihydroxy-5,6-dihydro-β-ionol [24], dihydrophaseic acid[25], blumenol A[26], isovitexin[27], daidzin[28], vitexin[29], and quercetin[30] were characterized by comparison of their physical and spectroscopic data with those reported in the literature.

Materials and Method

1. Softwares and programs

The ligand compounds were shown using the chemical molecular sketching program Chemsketch[33]. The.mol file was converted to.pdb format using Avogadro software[34] . Autodock 4.0 is [35]. For the semi-flexible protein ligand docking research, a preliminary docking software was employed. The chemical characteristics of the molecule were investigated using the Molinspiration online property calculator.[36] From the protein database, the crystalline structure of cyclooxygenase-2 was retrieved. Its PDB code was [PDB: 2YDV]. For computational investigations, this will serve as the goal. To virtually screen a library of derivatives, Pyrx software was employed.[37] Molecular interaction and visualization were performed using Discovery Studio 3.5.[11]

2. Preparation of ligand

With the help of the clean structure tool, the program Chemsketch was used to create the structure of the ligand. In the working folder, the structure was saved as a.mol file. Then, using the Avogadro program, the.mol file was accessed, and the structure was optimized. The working directory's.pdb file was used to save the optimized structure.

3. Preparation of receptor

With the help of Autodock v4.0 software, the crystal structure of the anti-inflammatory drug was corrected after being obtained in.pdb format from an internet database. Spreading the charges throughout the receptor reduced the energy. Polar hydrogen molecules were introduced, replacing the water molecules linked to the receptor.

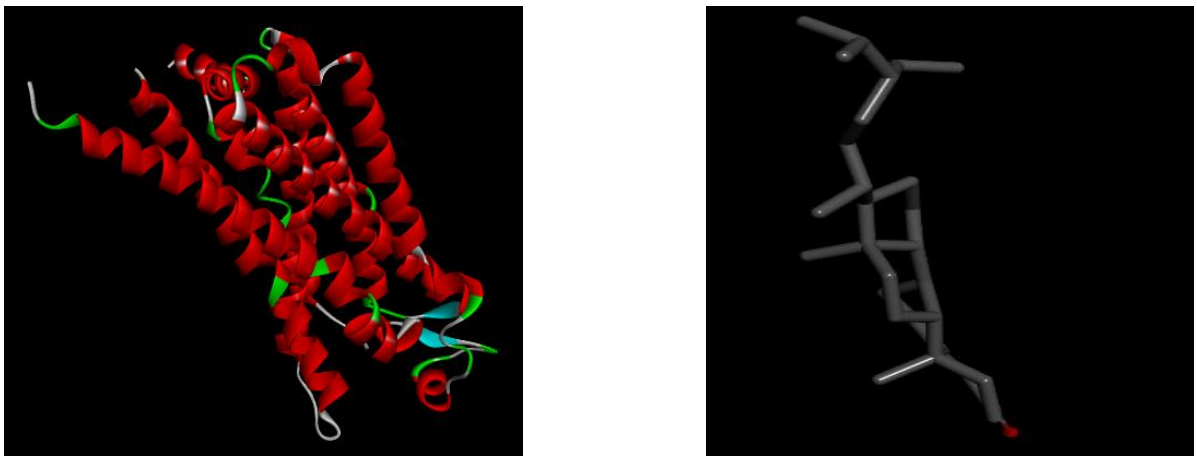

Fig.1: preparation of receptor and preparation of ligand

4. Receptor-Ligand Docking

We found binding positions and their corresponding binding energies using Autodock v4.0. According to the inverse relationship between energy and stability, a conformation with more binding energy is less stable. The default software program settings have been implemented in a manner consistent with other locations' usage of the protocol [12]. In a nutshell, the Lamarckian Genetic Algorithm (LGA) [13] was used to score energy, with co-ordinates of X = 24.320, Y = 25.140, and Z = 26.480 and a grid point spacing of 0.375 angstroms. The default atomic salvation parameters were 126 (x, y, and z) grid box in the ratio of (60:60:60). When creating the grid box, care was taken to position the 3D grid box so that the active ligand binding region of the receptor was in the middle and surrounded by the grid.

5. Online chemical property calculator

The Molinspiration online property calculator was used to calculate the properties of the ligand. An internal tool was used to sketch the structure of the ligand and determine a number of characteristics. Broad categories were employed to group the qualities, including structural property and bioactivity. Acute oral toxicity was expected when using the Protox II web server.[36]

Table 1: results of binding affinity of molecule and physiochemical properties and lipinski rules.

Sr. No.	Ligand	Docking score(kcal /mol)	MW (g/mol)	Rotatable bonds	H-bond acceptor	H-bond donors	TPSA	LOGP	Follow Lipinski
1.	Standard Caffeine	-6	194.08	0	6	0	61.82	0.048	Accepted
2.	**Stigmast-4-en-3-one**	**-10.8**	**412.37**	**6**	**1**	**0**	**17.07**	**8.044**	**Accepted**
3.	Daidzein	-9	254.06	1	4	2	70.67	2.795	Accepted
4.	5,7,4'-trihydroxy-3'-methoxy isoflavone	-8.8	314.08	3	6	2	89.13	2.732	Accepted
5.	Lupeol	-8.4	426.39	1	1	1	20.23	6.804	Accepted
6.	Sitosterol ferulate	-8.3	590.43	11	4	1	55.76	9.289	**Rejected**

7.	Stigmast-4,22-dien-3-one	-8.1	410.35	5	1	0	17.07	7.477	Accepted
8.	Abscisic acid	-7.2	264.14	3	4	2	74.6	2.342	Accepted
9.	Stigmasterol	-7.1	412.37	5	1	1	20.23	7.5	Accepted
10.	*Trans*-methyl *p*-coumarate	-7	412.37	5	1	1	20.23	7.5	Accepted
11.	*Trans*-cinnamic acid	-6.9	178.06	3	3	1	46.53	2.325	Accepted
12.	Methylparaben	-5.9	148.05	2	2	1	37.3	1.97	Accepted
13.	*P*-hydroxybenzoic acid	-5.8	152.05	2	3	1	46.53	1.84	Accepted

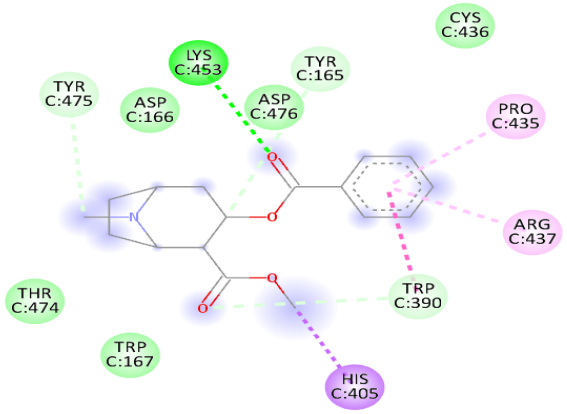

Fig. 2: 2D- interaction of standard caffeine with 2ydv receptor

The **standard Caffeine** binds an active site of **2YDV** with the lowest binding energy of **–6 Kcal/mol**, whereas, Conventional Hydrogen bond interaction LYS C:453 Pi- Sigma interaction with PRO C:435 , Pi- Pi Stacked and Pi- Alkyl interaction ARG C:437 and HIS C:405 and Van der Waals Interaction TYR C:475,ASP C:166,ASP C:476, TYR C:165,CYS C:436,TRP C:390,TRP C:167 and THR C:474 amino acid residue (Fig. 3).

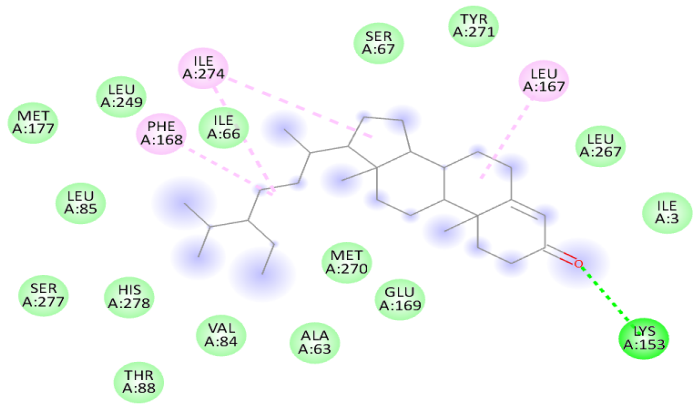

Fig.3 : 2D- interaction of stigmast-4-en-3-one with 2ydv receptor

Stigmast-4-en-3-one the best binding affinity of the chemical constituent **-10.8** and interaction of receptor and ligand molecule with interactions amino acid is conventional hydrogen bond LYS A:153 and alkyl and Pi-Alkyl interaction is ILE A:274,PHE A:168 and LEU A:167 and Van der Waals interaction is SER A:67, TYR A:271,LEU A:267, A:66, LEU A:249,ET A:177,LEU A:85,SER A:277,HIS A:278,VAL A:84,THR A88 interaction with amino acid.

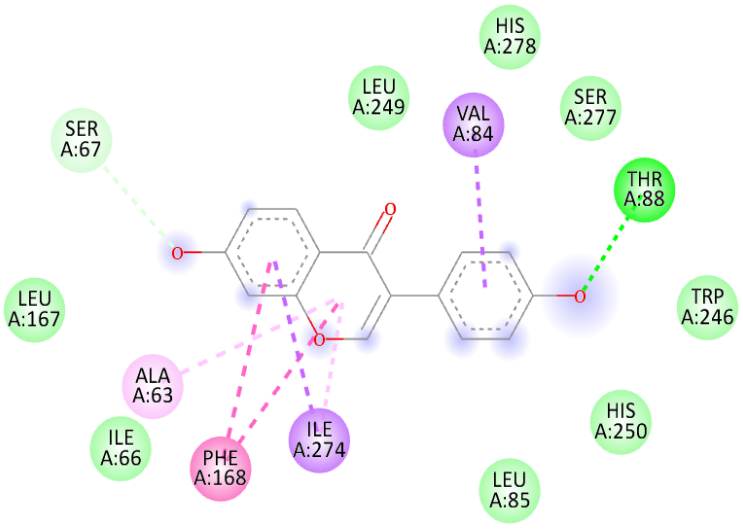

Fig.4 : 2D- interaction of daidzein with 2ydv receptor

Daidzein the best binding affinity of the chemical constituent **-9** and interaction of receptor and ligand molecule with interactions amino acid is conventional hydrogen bond THR A:88 and alkyl and Pi-Alkyl interaction is VAL A:84, ILE A:274, ALAA:63 and PHE A:168 and Van der Waals interaction is SER A:67, LEU A: 167, A 85,ILE A:66 HIS A:250 TRP A:246,SER A277,HIS A:278 and LEU A:24,interaction with amino acid.

3. ADMET Predications of the all chemical constituents with comparisons with the standard drug.

Table 2: Absorption of the all chemical constituents with standard drug.

Sr. No.	Ligand	Caco-2 Permeability	MDCK Permeability	Pgp-inhibitor	Pgp-substrate	HIA	$F_{20\%}$	$F_{30\%}$
1.	Standard Caffeine	-5.277	1.02E-05	0.359	0.751	0.011	0.003	0.034
2.	Stigmast-4-en-3-one	-4.783	8.31E-06	0.957	0.002	0.002	0.978	0.931
3.	Daidzein	-4.643	1.22E-05	0.006	0.937	0.008	0.23	0.856
4.	5,7,4'-trihydroxy-3'-methoxy isoflavone	-4.761	1.41E-05	0.004	0.976	0.014	0.004	0.03
5.	Lupeol	-5.208	2.84E-05	0.018	0	0.003	0.534	0.841
6.	Sitosterol ferulate	-4.813	1.93E-05	1	0.047	0.002	0.737	0.203
7.	Stigmast-4,22-dien-3-one	-4.614	1.13E-05	0.975	0.024	0.008	0.992	0.954
8.	Abscisic acid	-5.187	2.48E-05	0.001	0.026	0.021	0.003	0.001
9.	Stigmasterol	-4.576	1.44E-05	0.951	0.936	0.009	0.992	0.552
10.	*Trans*-methyl *p*-coumarate	-4.576	1.44E-05	0.951	0.936	0.009	0.992	0.552
11.	*Trans*-cinnamic acid	-4.512	2.17E-05	0.001	0.029	0.009	0.059	0.83
12.	Methylparaben	-4.657	1.43E-05	0	0.004	0.016	0.015	0.499
13.	*P*-hydroxybenzoic acid	-4.418	2.04E-05	0	0.002	0.006	0.003	0.915

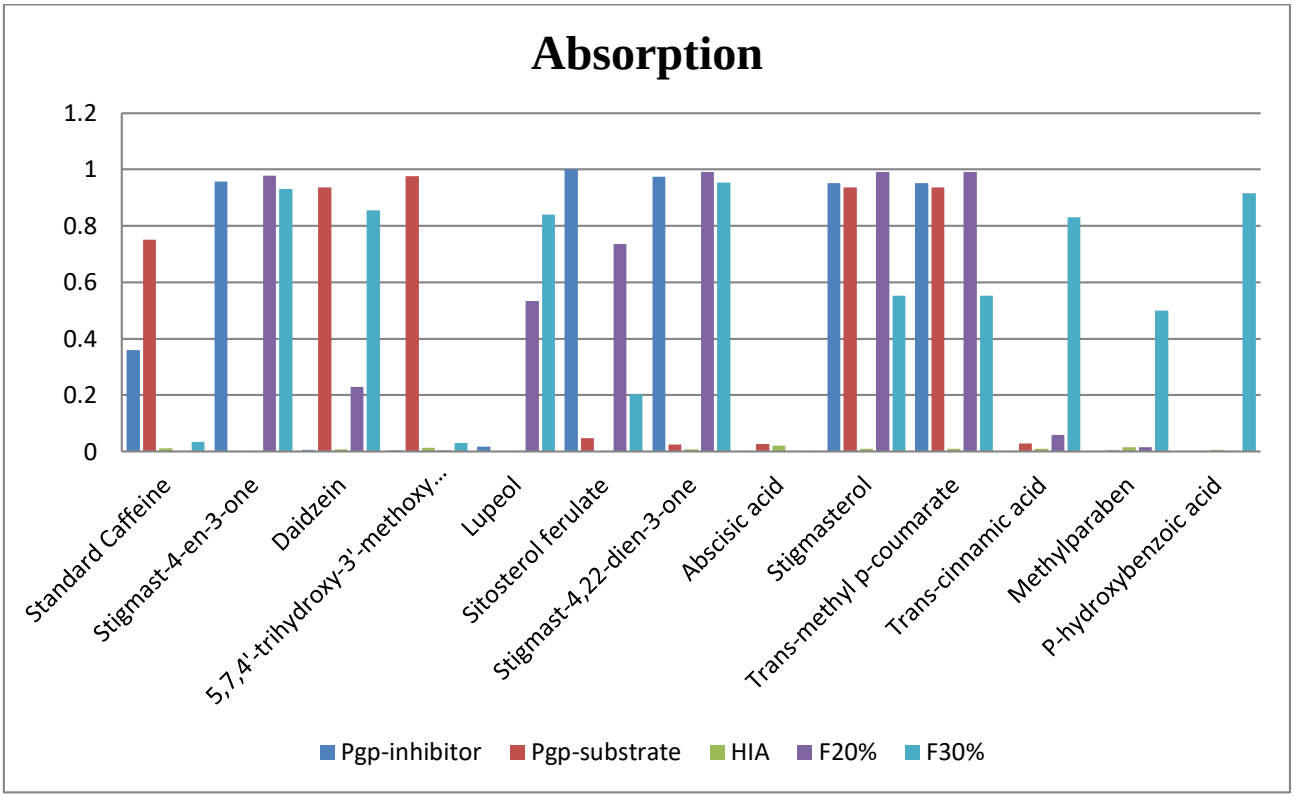

Fig 5: Absorption of the all chemical constituents with standard drug with graphical representation.

Table 3:Metabolism of the all chemical constituents with standard drug.

Sr. No.	Ligand	CYP1A2 -inh	CYP1A2 -sub	CYP2C19 -inh	CYP2C19 -sub	CYP2C9 -inh	CYP2C9 -sub	CYP2D 6-inh
1.	Standard Caffeine	0.135	0.974	0.024	0.312	0.003	0.545	0.002
2.	Stigmast-4-en-3-one	0.092	0.546	0.196	0.924	0.247	0.301	0.111
3.	Daidzein	0.976	0.127	0.808	0.054	0.375	0.945	0.929
4.	5,7,4'-trihydroxy-3'-methoxy isoflavone	0.96	0.931	0.743	0.062	0.712	0.926	0.847
5.	Lupeol	0.045	0.606	0.088	0.957	0.115	0.654	0.053
6.	Sitosterol ferulate	0.053	0.57	0.325	0.9	0.176	0.861	0.414
7.	Stigmast-4,22-dien-3-one	0.096	0.626	0.22	0.904	0.394	0.183	0.239
8.	Abscisic acid	0.012	0.334	0.048	0.087	0.355	0.613	0.004
9.	Stigmasterol	0.093	0.651	0.17	0.924	0.346	0.083	0.295
10.	*Trans*-methyl *p*-coumarate	0.093	0.651	0.17	0.924	0.346	0.083	0.295
11.	*Trans*-cinnamic acid	0.972	0.65	0.781	0.33	0.422	0.924	0.055
12.	Methylparaben	0.172	0.069	0.04	0.055	0.091	0.754	0.048
13.	*P*-hydroxybenzoic acid	0.938	0.771	0.616	0.135	0.173	0.912	0.122

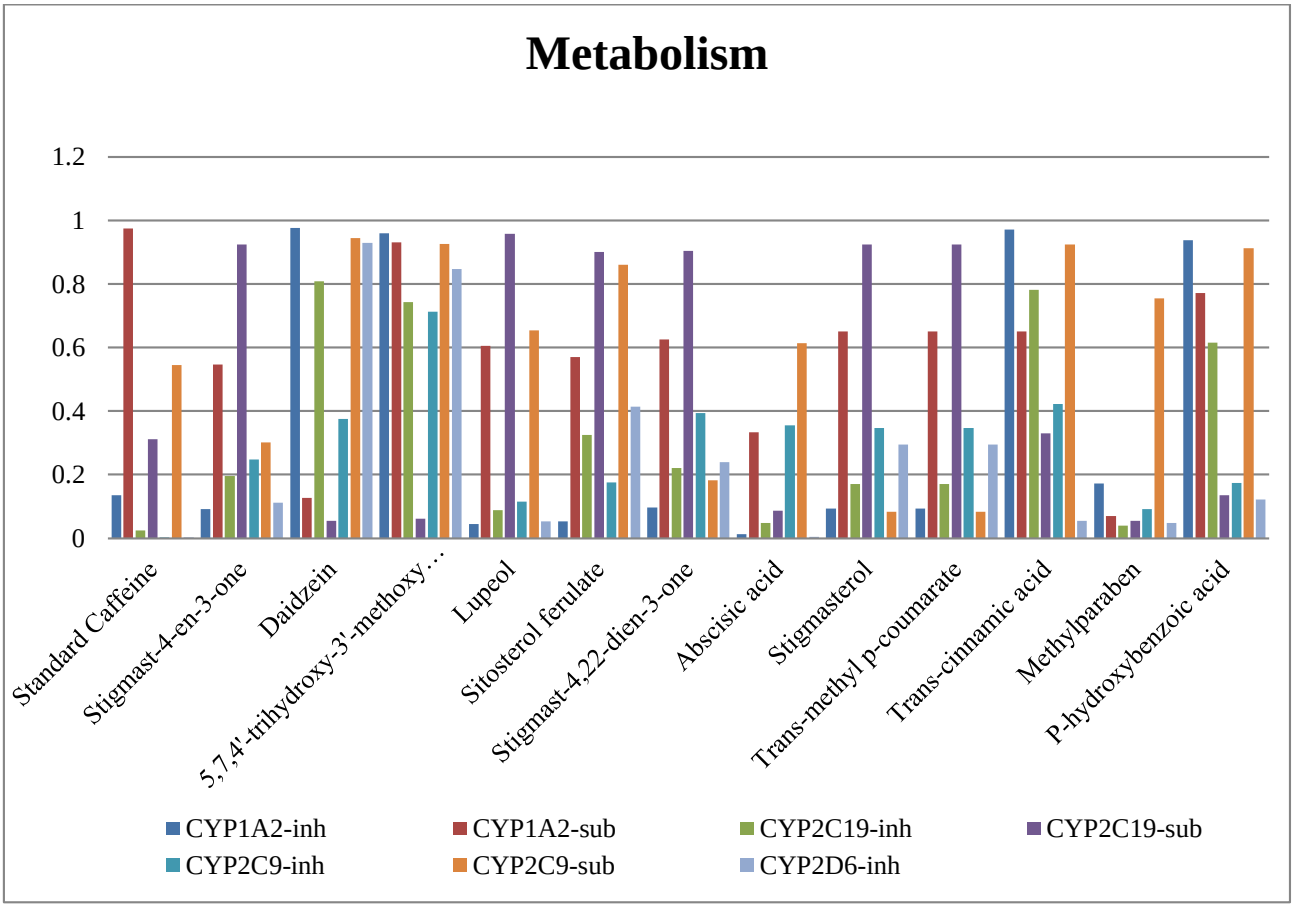

Fig.6: Metabolism of the all chemical constituents with standard drug with graphical representation.

Table 4: Excretion of the all chemical constituents with standard drug.

Sr. No.	Ligand	CL	T12
1.	Standard Caffeine	1.83	0.774
2.	Stigmast-4-en-3-one	6.383	0.172
3.	Daidzein	7.802	0.846
4.	5,7,4'-trihydroxy-3'-methoxy isoflavone	7.491	0.864
5.	Lupeol	4.161	0.151
6.	Sitosterol ferulate	6.179	0.049
7.	Stigmast-4,22-dien-3-one	4.014	0.128
8.	Abscisic acid	1.678	0.881
9.	Stigmasterol	4.515	0.036
10.	*Trans*-methyl *p*-coumarate	4.515	0.036
11.	*Trans*-cinnamic acid	12.352	0.916
12.	Methylparaben	2.795	0.855
13.	*P*-hydroxybenzoic acid	13.9	0.905

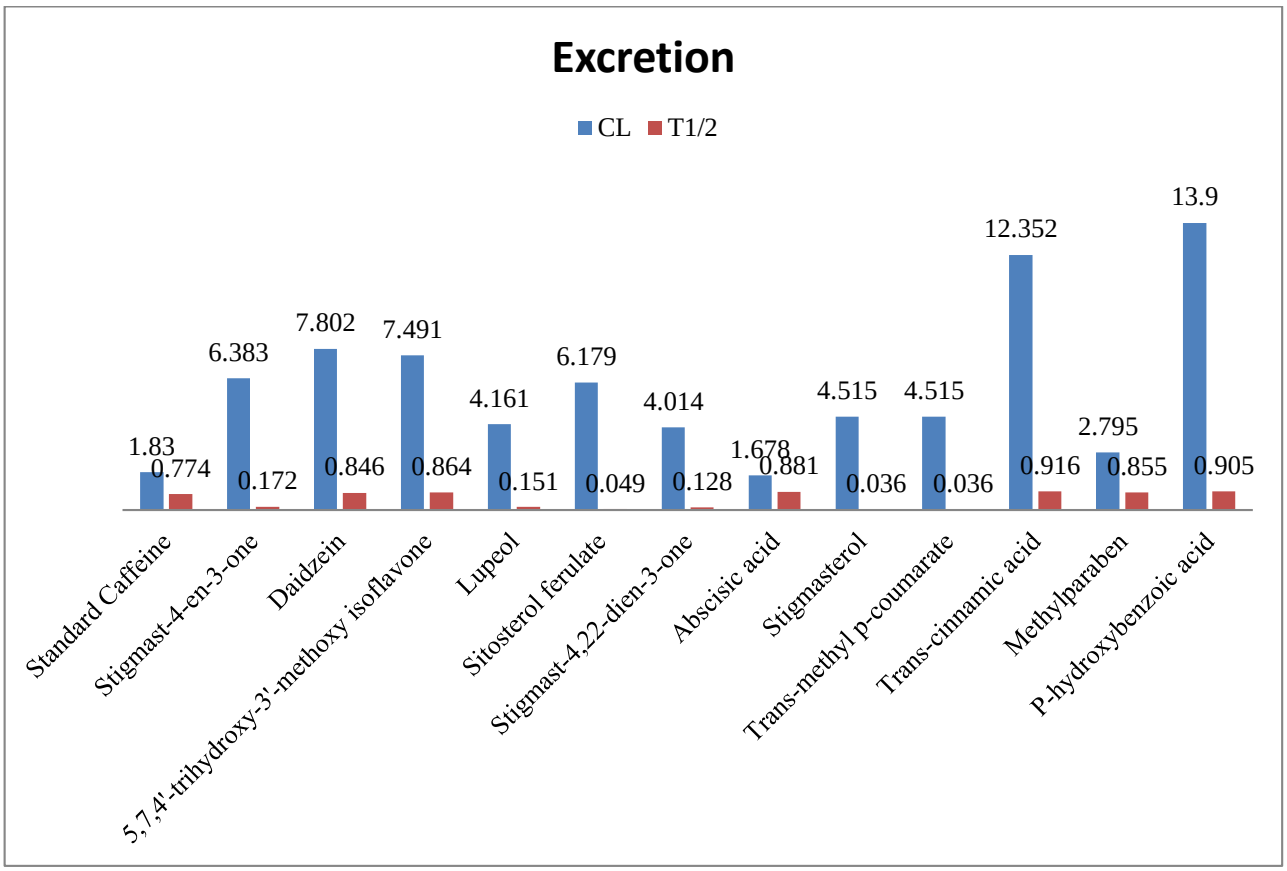

Fig 7: Excretion of the all chemical constituents with standard drug with graphical representation.

Table 5: Toxicity predication of the all chemical constituents with standard drug.

Sr. No.	Ligand	Carcinogenicity	Skin_Sensitization	Acute_Aquatic_Toxicity	Toxicophores
1.	Standard Caffeine	0.039	0	0	1
2.	Stigmast-4-en-3-one	0.131	1	1	0
3.	Daidzein	0.617	0	0	1
4.	5,7,4'-trihydroxy-3'-methoxy isoflavone	0.108	5	0	1
5.	Lupeol	0.002	0	1	0
6.	Sitosterol ferulate	0.091	7	3	2
7.	Stigmast-4,22-dien-3-one	0.121	1	1	0
8.	Abscisic acid	0.375	4	4	2
9.	Stigmasterol	0.1	0	1	0
10.	*Trans*-methyl *p*-coumarate	0.1	0	1	0
11.	*Trans*-cinnamic acid	0.474	3	3	2
12.	Methylparaben	0.091	2	2	1
13.	*P*-hydroxybenzoic acid	0.162	0	0	1

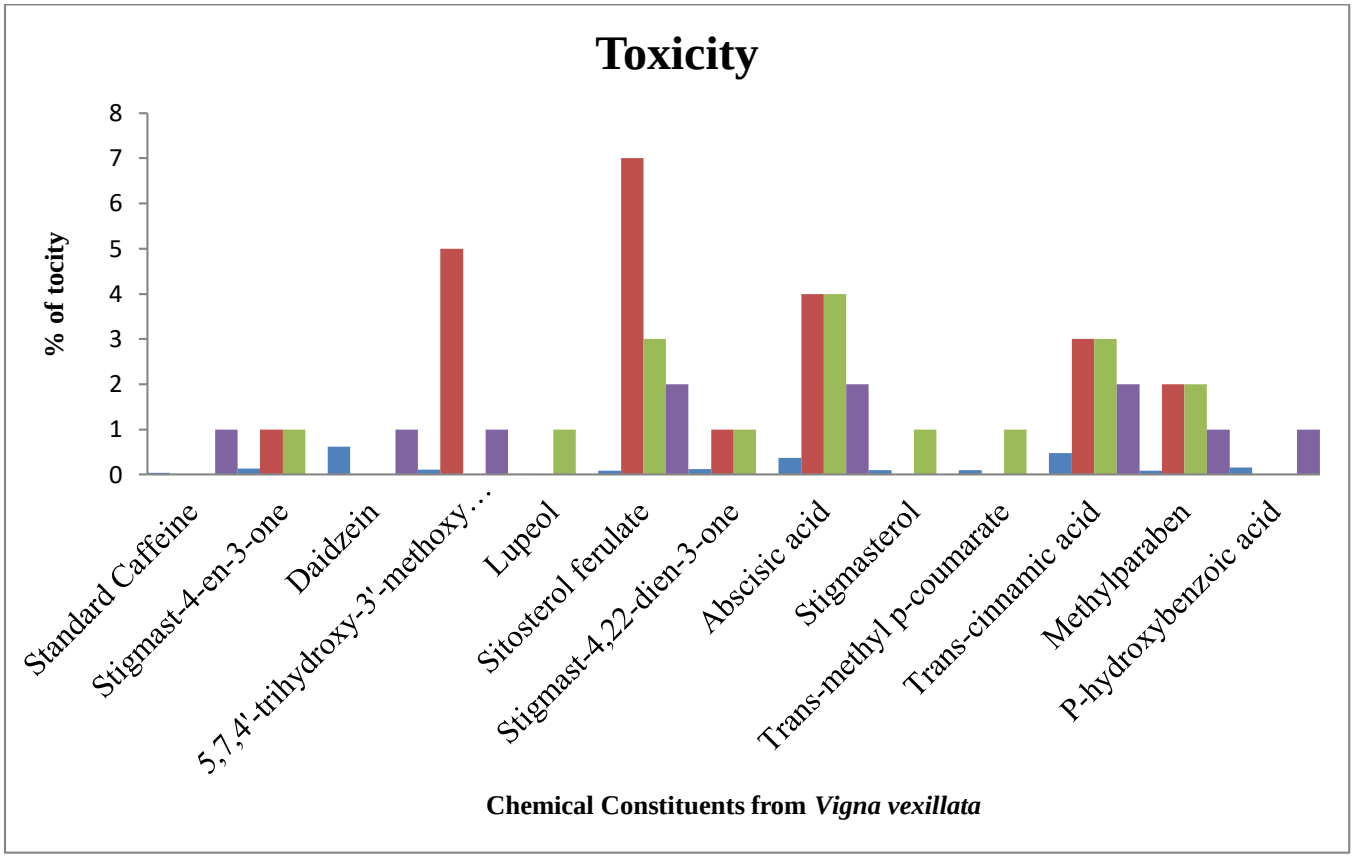

Fig 8: Toxicity predication of the all chemical constituents with standard drug with graphical representation.

Conclusion

The study showed Stigmast-4-en-3-one best binding affinity of natural chemical constituent was best interaction with receptor **(CNS Stimulant activity of the code of the receptor is PDB ID :2YDV)** and comparison study with **standers drug is caffeine** having binding affinity is **-6kcal/mol** and the **Stigmast-4-en-3-one** binding affinity of the naturally obtaining chemical constituents is **-10.8kcal/mol.** This drug is used as a CNS stimulant like work according to the molecular docking and ADMET predication and interactions with active sites. These enabled us to validate the molecule's effectiveness in treating CNS stimulant receptors.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CONFLICT OF INTEREST STATEMENT

All authors declare no conflict of interest.

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