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IN-SILICO STUDIES, CHARACTERIZATION, ADMET PREDICTION AND MOLECULAR DOCKING OF *WEDELIA CHINENSIS* CONSTITUENTS AND THEIR CNS STIMULANT ACTIVITY

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Abstract: *Wedelia chinensis* Merrill (Syn. *Wedelia calendulaceae*, *Solidogo chinensis*) (Asteraceae, Sunflower family) is a small much branched annual herb, commonly known as "Pilabhangara" or "Bringraj" in hindi. *Wedelia* in chinese, Pitabhamga, Pitabhmgaraj in Sanskrit. *Wedelia chinensis* is a tender, spreding and hairy herb, with the branches usually less than 50cm long.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 Alzheimer's 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.

***Index Terms*:** *Wedelia chinensis* , Standard caffeine, Molecular Docking, PyRx Vina auto dock, Chemsketch, ADMET Prediction.

I. INTRODUCTION

Wedelia chinensis Merrill (Syn. *Wedelia calendulaceae, Solidogo chinensis*) (Asteraceae, Sunflower family) is a small much branched annual herb, commonly known as "Pilabhangara" or "Bringraj" in hindi. *Wedelia* in chinese, Pitabhamga, Pitabhmgaraj in Sanskrit. *Wedelia chinensis* is a tender, spreding and hairy herb, with the branches usually less than 50cm long [1].

I.I Taxonomical Classification:

Common Name: Bhringraj
Botanical name: *Wedelia chinensis*
Kingdom: Plantae
Order: Asterales
Family: Asteraceae.
Subfamily: Asteroideae
Tribe: Heliantheac
Subtribe: Ecliptinac
Genus: *Wedelia*
Species: *chinensis*

Fig No 1: *Wedelia chinensis*

Wedelia chinensis is a perennial herb that ranges in height from 0.3 to 0.9 cm. The leaves are succulent, often 4–9 cm long and 2–5 cm broad, irregularly serrated or serrate, and obviate in form. They also typically have two lateral lobes. Flowers have a diameter of 4-5 cm, are tubular, and are found in terminal or axillary heads [1]. The fruits, leaves, and stem are traditionally used in childbirth, the treatment of bites and stings, fever, and illness. The leaves are applied topically to wounds and to cure amenorrhea, colds, and renal problems [2]. In the ayurvedic, siddha, and unani systems of medicine, *Wedelia chinensis* is a commonly used medicinal herb [3]. Cough and cephalagia are treated with the leaf tonic. Menorrhagia and skin conditions are treated with the plant's decoction [4]. The herb has also been effective in treating liver ailments, helminthic infections, and inflammations [5]. Antioxidant properties of the plant have been scientifically shown, indicating their value in easing emotional states such as anxiety and stress [6]. *Wedelia chinensis* is one of the most widely used herbal medicines in many different medical systems, including Ayurvedic, Siddha, and Unani system of medicine [7]. Alkaloids, saponins, tannin, flavonoids, a lactone, wedelolactone, and norwedilic acid are all present in the plant. *Wedelia chinensis*'s expressed juice includes waxy substances, phytosterols, carotene, resin, and an oil-soluble black pigment. Inorganic salts, siliceous compounds, pectin, and mucin are also present in the plant [8]. Wedelolactone (I) (0.05%) and isoflavanoids are present in the leaves. The latter is the lactone of 5:6-dihydroxy-2- (2:6-dihydroxy-4-methoxyphenyl) benzofuron-3-corboxylic acid, and it resembles coumestrol, an oestrogen from clover, in terms of structure [9, 10, 11, 12]. The leaves also include wedelolactones and bisdesmosidic oleanolic acid saponins [12, 13, 14, 15]. Additionally, norwedelolactone (II) has been extracted from an alcoholic leaf extract [12, 16]. Norwedelic acid (III) (5, 6-dihydroxy-2 (2', 4', 6'- trihydroxyphenyl)-benzofuran-3-carboxylic acid) [12, 13].The herb has been used traditionally for a variety of ailments, including jaundice, amenorrhea, dying hair, multiple sclenosis, renal illness, colds, wound healing, amenorrhea, and skin conditions like cephalegia and apopecia.

II. MATERIALS AND METHOD

II. I. Softwares and programs

The ligand compounds were shown using the chemical molecular sketching program Chemsketch[19]. The.mol file was converted to.pdb format using Avogadro software[20] . Autodock 4.0 is [16]. 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.[21] 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.[23] Molecular interaction and visualization were performed using Discovery Studio 3.5.[24]

II. II. 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.

II. III. Preparation of receptor

With the help of Autodock v4.0 software, the crystal structure of the CNS Stimulant 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[20].

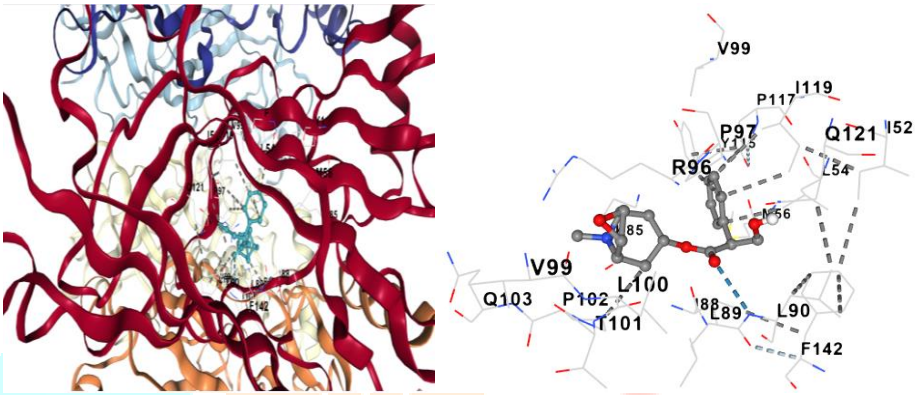

Fig. 2: Preparation of receptor and preparation of ligand

II. IV. 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. In a nutshell, the Lamarckian Genetic Algorithm (LGA) 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.

II. V. 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.[22]

Table 1: Results of binding affinity of molecule and physiochemical properties and Lipinski rules.

Sr. No.	Ligand	Docking score	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.	Stigmasterol	-10.7	412.37	5	1	1	20.23	7.436	Accepted
3.	Wedelolactone	-10	314.04	1	7	3	113.27	3.194	Accepted
4.	Luteolin	-9.5	286.05	1	6	4	111.13	2.902	Accepted
5.	Quercetin	-9.3	302.04	1	7	5	131.36	2.155	Accepted
6.	ρ- Cymene	-7.1	134.11	1	0	0	0	3.994	Accepted
7.	a-humulene	-7	204.19	0	0	0	0	5.194	Accepted
8.	Stigmasteryl glucoside	-7	574.42	8	6	4	99.38	5.738	**Rejected**
9.	Germacrene	-6.7	206.2	1	0	0	0	5.393	Accepted
10.	Indole-3-carbaldehyde	-6.7	145.05	1	2	1	32.86	2.02	Accepted
11.	Norwedelic acid	-6.7	318.04	2	8	6	151.59	2.041	Accepted
12.	Phenacetin	-6.6	179.09	4	3	1	38.33	1.677	Accepted
13.	Lignoceric acid	-6.4	368.37	22	2	1	37.3	9.98	Accepted
14.	Melissic acid	-6.4	452.46	28	2	1	37.3	12.313	Accepted
15.	Spathulenol	-6.3	220.18	0	1	1	20.23	4.032	Accepted
16.	Phellandrene	-5.7	136.13	1	0	0	0	3.857	Accepted
17.	Limonene	-5.2	136.13	1	0	0	0	4.368	Accepted

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	-4.668	7.52E-06	0.066	0.001	0.005	0.008	0.185
2.	Stigmasterol	-5.096	1.15E-05	0.009	0.868	0.154	0.042	0.998
3.	Wedelolactone	-5.028	1.00E-05	0.004	0.274	0.047	0.998	1
4.	Luteolin	-5.204	7.69E-06	0.004	0.005	0.014	0.93	0.997
5.	Quercetin	-4.302	1.96E-05	0.011	0.005	0.004	0.211	0.931
6.	ρ- Cymene	-4.613	1.64E-05	0.068	0.001	0.016	0.012	0.003
7.	a-humulene	-4.816	2.10E-05	0.051	0.004	0.035	0.012	0.17
8.	Stigmasteryl glucoside	-4.539	2.04E-05	0.092	0.005	0.008	0.94	0.975
9.	Germacrene	-4.492	9.89E-06	0	0.004	0.008	0.011	0.967
10.	Indole-3 carbaldehyde	-6.127	5.46E-06	0	0.013	0.591	0.996	1
11.	Norwedelic acid	-4.298	1.71E-05	0.003	0.063	0.003	0.003	0.993
12.	Phenacetin	-5.196	1.04E-05	0	0	0.005	0.258	0.999
13.	Lignoceric acid	-5.272	3.82E-06	0	0	0.006	0.124	1
14.	Melissic acid	-4.567	1.93E-05	0.001	0	0.004	0.008	0.012
15.	Spathulenol	-4.383	2.39E-05	0.001	0.013	0.005	0.014	0.146
16.	Phellandrene	-4.32	1.93E-05	0.002	0	0.003	0.818	0.798
17.	Limonene	-4.668	7.52E-06	0.066	0.001	0.005	0.008	0.185

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	CYP2D6-inh
1.	Standard caffeine	0.135	0.974	0.024	0.312	0.003	0.545	0.002
2.	Stigmasterol	0.981	0.862	0.076	0.057	0.615	0.908	0.282
3.	Wedelolactone	0.981	0.154	0.124	0.046	0.576	0.842	0.568
4.	Luteolin	0.943	0.115	0.053	0.041	0.598	0.643	0.411
5.	Quercetin	0.941	0.944	0.855	0.864	0.574	0.61	0.778
6.	ρ- Cymene	0.691	0.515	0.529	0.426	0.429	0.948	0.728
7.	a-humulene	0.002	0.337	0.007	0.891	0.035	0.106	0.001
8.	Stigmasteryl glucoside	0.441	0.502	0.326	0.361	0.535	0.917	0.177
9.	Germacrene	0.977	0.45	0.559	0.285	0.12	0.911	0.081
10.	Indole-3-carbaldehyde	0.492	0.071	0.026	0.034	0.424	0.126	0.038
11.	Norwedelic acid	0.841	0.94	0.479	0.824	0.065	0.843	0.033
12.	Phenacetin	0.102	0.155	0.214	0.054	0.051	0.995	0.028
13.	Lignoceric acid	0.046	0.127	0.108	0.046	0.02	0.997	0.042
14.	Melissic acid	0.139	0.587	0.085	0.895	0.227	0.604	0.009
15.	Spathulenol	0.258	0.471	0.178	0.93	0.142	0.337	0.059
16.	Phellandrene	0.678	0.652	0.223	0.834	0.06	0.804	0.02
17.	Limonene	0.678	0.652	0.223	0.834	0.06	0.804	0.02

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

Sr. No.	Ligand	CL	T1/2
1.	Standard caffeine	1.83	0.774
2.	Stigmasterol	15.958	0.014
3.	Wedelolactone	8.454	0.819
4.	Luteolin	8.146	0.898
5.	Quercetin	8.284	0.929
6.	ρ- Cymene	7.38	0.276
7.	a-humulene	3.4	0.403
8.	Stigmasteryl glucoside	4.455	0.017
9.	Germacrene	5.488	0.253
10.	Indole-3-carbaldehyde	6.548	0.798
11.	Norwedelic acid	9.177	0.938
12.	Phenacetin	6.297	0.684
13.	Lignoceric acid	2.761	0.21
14.	Melissic acid	2.897	0.079
15.	Spathulenol	14.582	0.064
16.	Phellandrene	12.66	0.617
17.	Limonene	11.517	0.233

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

Sr. No.	Ligand	Carcinogenicity	Skin Sensitization	Acute Toxicity	Aquatic	Toxicophores
1.	Standard caffeine	0.039	0	0		1
2.	Stigmasterol	0.054	0	1		0
3.	Wedelolactone	0.032	6	0		4
4.	Luteolin	0.095	7	0		2
5.	Quercetin	0.05	8	0		2
6.	ρ- Cymene	0.386	0	1		0
7.	a-humulene	0.028	0	1		0
8.	Stigmasteryl glucoside	0.045	1	2		0
9.	Germacrene	0.029	0	1		0
10.	Indole-3-carbaldehyde	0.25	2	0		3
11.	Norwedelic acid	0.029	7	0		3
12.	Phenacetin	0.783	4	0		1
13.	Lignoceric acid	0.03	0	0		0
14.	Melissic acid	0.02	0	0		0
15.	Spathulenol	0.065	0	1		0
16.	Phellandrene	0.344	0	1		0
17.	Limonene	0.922	0	1		0

III. CONCLUSION

The study showed **Stigmasterol** 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 **Stigmasterol** binding affinity of the naturally obtaining chemical constituents is **-10.7kcal/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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IV. REFERENCES

1. Umashankar K, Suresh V, Kumar R.M, Suresh A, Arunachalam G, CNS activity of ethanol extract of *Wedelia chinensis* in experimentals animals, International journal of pharmaceutical sciences and nanotechnology, 2010; 3: 113-543.
2. Mathew. K M. Flora of Tamilnadu-carnatic. The Rapinat Herbarium, St. Josephs College, Trichirapalli, 1983; 392.
3. Manjamlai. A, Jiflin G.J, Grace berlin V.M, Study on the effect of essential oil of *Wedelia Chinensis* against microbes and inflammation, Asian Journal of Pharmaceutical and Clinical Research., 2012; 5: 0974-2441.
4. Kirthikar K.R, Basu B.D. Indian Medicinal Plants. Dehradun: International Book Distributors, 2006; 1324-45.

5. Jalal A.A, Selvakumar. S, Nallathambi. R, Jeevaprakash. G, Dheivanai. S.L, Senthilvelan. S, Hepatoprotectiveactivity of *Wedelia chinensis* against carbon tetrachloride induced liver damage in rats, International Journal of Phytopharmacology., 2012; 3: 121-125.
6. Suresh. V, Kumar. R.M, Suresh. A, Kumar. N.S, Arunachalam. G, Umasankar. K, CNS Activity of Ethanol Extract of *Wedelia chinensis* in Experimental Animals,International Journal of Pharmaceutical Sciences and Nanotechnology, 2010; 3: 11.
7. Koul S , Pandurangan A, Khosa R.L, *Wedelia chinenis* (Asteraceae) - An overview Asian Pacific Journal of Tropical Biomedicine, 2012; S1169-S1175.
8. Ghani, A. Medicinal Plants of Bangladesh with chemical constituents and uses.2nd edition, Asiatic Society of Bangladesh, 5 old Secretariate road, Nimtali, Dhaka, Bangladesh, 2003.
9. Govindchari TR, Nagarajan K, Pai BR. Chemical examination of *Wedelia calendulaceae*, Structure of Wedelolactone. J Chem Soc., 1956; 629-632.
10. Govindchari TR, Nagarajan K, Pai BR, Parthasarathy PC. Chemical investigation of *Wedelia calendulaceae*, Part-II, The position of the methoxyl group in Wedelolactone. J Chem Soc;, 1957; 545-547.
11. Govindchari TR, Nagarajan K, Parthasarathy PC. Chemical examination of *Wedelia calendulaceae*-IV, Synthetic analogues of Wedelolactone. Tetrahedron, 1961; 15: 129-131.
12. Masoodi M.H, Ahmad B, Wali A.F, Zargar B.A, Dar M.A, Recent developments in phytochemical and pharmacological studies of *Wedelia calendulaceae*-A review. Indian J Nat Prod., 2011; 27: 3-7.
13. Govindachari TR, Premila MS, The benzofuran norwedelic acid from *Wedelia calendulaceae*. Phytochemistry, 1985; 24: 3068- 3069.
14. Khare C.P. Indian medicinal plants: An illustrated dictionary. Heidelberg: Springer; 2007; 716.
15. Haldar P.K, Bhattacharya S, Dewanjee S, Mazumdera U.K. Chemopreventive efficacy of *Wedelia calendulaceae* against 20- methylcholanthrene-induced carcinogenesis in mice. Environ Toxicol Pharmacol, 2011; 31: 10-17.
16. Bhargava K.K, Krishnaswamy N.R, Seshadri T.R. Isolation of dimethyl wedelolactone and its glucoside from *Eclipta alba*. Indian J Chem., 1970; 8: 664-665.
17. Wiley, C. A., Lopresti, B. J., Venneti, S., Price, J., Klunk, W. E., DeKosky, S. T., & Mathis, C. A. (2009). Carbon 11–labeled Pittsburgh compound b and carbon 11–labeled (R)-PK11195 positron emission tomographic imaging in Alzheimer Disease. *Archives of neurology*, *66*(1), 60-67.[PMC free article] [PubMed] [Google Scholar]
18. Roe, C. M., Mintun, M. A., D'Angelo, G., Xiong, C., Grant, E. A., & Morris, J. C. (2008). Alzheimer disease and cognitive reserve: variation of education effect with carbon 11–labeled Pittsburgh Compound B uptake. *Archives of neurology*, *65*(11), 1467-1471. [PMC free article] [PubMed] [Google Scholar]
19. Chemsketch : http://www.acdlabs.com(Web server issue 2014)
20. Avogadro : http://avogadro.cc (Web server issue 2010)
21. Autodock v4.0 : http://autodock.scripps.edu(Web server issue 2014)
22. Molinspiration online property calculator : https://www.molinspiration.com(Web server issue 2018)
23. pyrex : http://www.pyrex.cc(Web server issue 2010)
24. Discovery Studio 3.5 https://discover.3ds.com/discovery-studio-visualizer-download