In-Silico Studies, Characterization, ADMET Prediction, and Molecular Docking of *Plumeria Rubra Linn* Constituents and Their Alzheimer's Activity

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ABSTRACT

The Apocynaceae family includes the laticiferous trees and bushes known as Plumeria rubra L (also known as Lal champa in Hindi and True Frangipani in English). In the tropical and subtropical parts of the world, these species' plants are widely farmed. The usage of leaves includes stimulant, antipyretic, antifungal, antibacterial, bronchitis, cholera, colds, and coughs.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.

Keywords: *Plumeria rubra; Lepeol, Molecular Docking, PyRx Vina auto dock, Chemsketch, ADMET Prediction.*

1. INTRODUCTION

The Apocynaceae family includes the laticiferous trees and bushes known as *Plumeria rubra* L (also known as Lal champa in Hindi and True Frangipani in English). In the tropical and subtropical parts of the world, these species' plants are widely farmed.[1] They are well-known for being top-notch attractive plants and are frequently spotted in cemeteries.[2] Flowers on plants are renowned for their beauty and fragrance. For the purposes of aromatherapy and fragrance, the flowers' essential oils are employed. Traditional remedies for asthma, constipation, promoting menstruation, and lowering fever include a decoction made from *Plumeria rubra's* bark and roots. To relieve irritability, latex is utilized.[3] It is said that the fruit is consumed in the West Indies. But it has been employed as an abortion inducer in India.[4] A common ingredient in pectoral syrups, the blooms have a pleasant perfume. According to reports, Mexico uses P. rubra's flower decoction to manage type 2 diabetes. Leprosy, inflammations, and ulcers can all be treated using P. rubra leaves.[5]A dense deciduous tree, *Plumeria rubra* Linn. For a brief period in the winter, a plant loses its leaves. Up to 25 feet tall, it can grow. There is sluggish plant growth. India has around eight different varieties of *Plumeria rubra* (L.). Simple alternating, spiral, undissected petiole, elliptic or oval form, base tapering (narrow attenuate), entire or undulate margins, and acuminate, acute, or obtuse apex are the characteristics of ascending leaves. Flowers with red or pink hues and spreading cymes with long fruits are seen.[6] August to October is when plants bloom. Ayurveda claims that the root is bitter, laxative, thermo genic, carminative, leprous, etc. The usage of leaves includes stimulant, antipyretic, antifungal, antibacterial, bronchitis, cholera, colds, and coughs.[7][8]

1.1 Taxonomical Clssification

Common Name : Frangipani
Vernacular Name : Mar - Lal champa
English: Frangipani
Kingdom: Plantae
Subkingdom: Tracheobionta
Superdivision: Spermatophyta
Division: Magnoliophyta
Class: Dicotyledons
Subclass: Asteridae
Order: Gentiales
Family: Apocynaceae
Botanical Name: *Plumaria rubra*
Plant Type: shrub
Origin: India, Sri Lanka [9]

1.2 Chemical Constituents

Iridoids such plumericin, fulvoplumierin, allamandin, Alpha- and beta-allamcidin, plumieride, 15-Demethylplumieride, 13-O-trans-p-Coumaroylplumieride lignan, liriodendrin, and 2,5-dimethoxy-p-benzoquinone. A, B, and C plumeridoids, C the epiplumeridioid, Isoplumericin and dihydroplumericin, 1-(P-hydroxyphenyl) propan-1-one, the P-E coumaric acid, 2,6-dimethoxy-P-benzoquinone, scopoletin, cycloart-25-en-3 beta 24-diol, 2,4,6-trimethoxyaniline, beta-amyrin acetate, betulinic acid, lupeol and its acetate, ajunolic acid, ursolic acid, oleanolic acid, and cycloart-25-en-3 beta 24-diol, 2,3-dihydroxypropyl octacosanoate, stigmasterol, beta-sitosterol, and their glucosides, 2-methylbutan-1-ol, -phenyl ethyl alcohol, nanodecane, heneicosane, benzyl salicylate,

octadecanoic acid, tetradeconoic acid, and phenylacetaldehyde 2,4,6-trimethoxyaniline, 3-O-caffeoylquinic acid, betulinic acid, citric acid, gaertneroside, kaempferol, kaempferol-3-rutinoside, kaempferol-3-O-glucoside, lupeol, lupeol acetate, lupeol carboxylic acid, maslinic acid, methyl salicylate[10].The compounds P-(E)-coumaric acid, plumericidine, plumerinine, plumerubroside, and plumierideE-p-coumarate, quercetin 3-O-L arabinopyranoside, quinic acid, rubradoid, rubrajaleelol, rubrajaleelic acid, rubranonoside, rutin, stigmast-7-enol, sweroside, and taraxasteryl acetate are some of the compounds that have been linked to health benefits[11].

2. MATERIALS AND METHOD

2.1. Softwares and programs

The ligand compounds were shown using the chemical molecular sketching program Chemsketch[14]. The.mol file was converted to.pdb format using Avogadro software[16] . 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.[17] From the protein database, the crystalline structure of cyclooxygenase-2 was retrieved. Its PDB code was [PDB: 5OUG]. For computational investigations, this will serve as the goal. To virtually screen a library of derivatives, Pyrx software was employed.[18] Molecular interaction and visualization were performed using Discovery Studio 3.5.[19]

2.2. 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.

2.3. Preparation of receptor

With the help of Autodock v4.0 software, the crystal structure of the Alzheimer's 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[16].

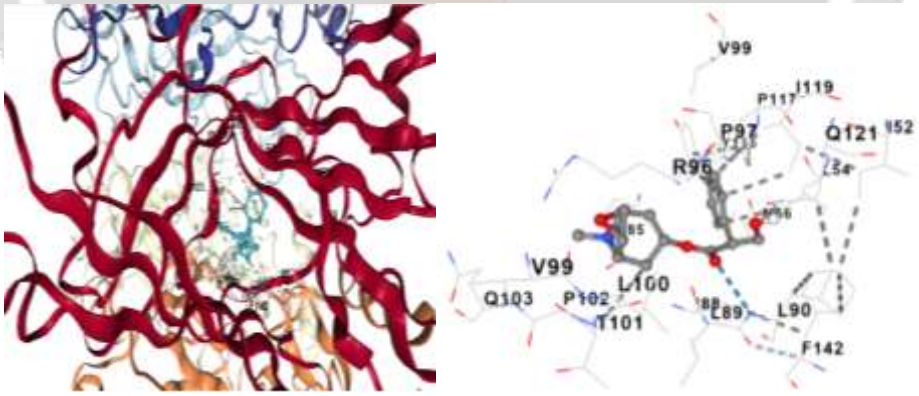

Fig.1: Preparation of receptor and preparation of ligand

2.4. 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 [16]. In a nutshell, the Lamarckian Genetic Algorithm (LGA) [17] 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.

2.5. 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.[17]

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 Scopolamine	-7.4	303.15	5	5	1	62.3	1.24	Accepted
2.	Lepeol	-9.6	426.39	1	1	1	20.23	6.804	Accepted
3.	Ursolic acid	-9.4	456.36	1	3	2	57.53	6.453	Accepted
4.	Betullinic acid	-9.3	456.36	1	3	2	57.53	5.867	Accepted
5.	Oleanolic acid	-9.1	456.36	1	3	2	57.53	6.645	Accepted
6.	Fulvoplumierin	-9.1	244.07	1	4	0	56.51	1.456	Accepted
7.	Arjunolic acid	-8.6	488.35	1	5	4	97.99	4.393	Accepted
8.	Isoplumericin	-8.3	290.08	1	6	0	71.06	1.683	Accepted
9.	Plumieride	-8	470.14	1	12	5	181.44	-0.25	Accepted
10.	Allamandin	-7.8	308.09	1	7	1	91.29	0.802	Accepted
11.	Lignan	-7.3	458.19	1	8	2	95.84	3.044	Accepted
12.	2,5-Dimethoxy-p-benzoquinone	-5.4	168.04	1	4	0	52.6	0.018	Accepted
13.	2,6-Dimethoxy-p-benzoquinone	-5.3	168.04	1	4	0	52.6	0.006	Accepted

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
1.	Standard Scopolamine	-4.986	0.000101	0.002	0.125	0.01
2.	Lepeol	-5.208	2.84E-05	0.018	0	0.003
3.	Ursolic acid	-5.396	1.03E-05	0.002	0	0.004
4.	Betullinic acid	-5.391	3.04E-05	0.002	0	0.004
5.	Oleanolic acid	-5.37	1.16E-05	0.001	0	0.012
6.	Fulvoplumierin	-4.762	1.90E-05	0.035	0.03	0.01
7.	Arjunolic acid	-5.435	1.41E-05	0.003	0	0.009
8.	Isoplumericin	-4.899	3.71E-05	0.001	0	0.011
9.	Plumieride	-5.841	0.000101	0.002	0.108	0.926
10.	Allamandin	-5.108	4.93E-05	0.317	0.006	0.013
11.	Lignan	-4.964	3.36E-05	0.876	0.804	0.011
12.	2,5-Dimethoxy-p-benzoquinone	-4.476	2.66E-05	0.094	0.001	0.006

13.	2,6-Dimethoxy-p-benzoquinone	-4.454	2.46E-05	0.166	0.001	0.009

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 Scopolamine	0.036	0.087	0.027	0.832	0.014	0.195	0.274
2.	Lepeol	0.045	0.606	0.088	0.957	0.115	0.654	0.053
3.	Ursolic acid	0.018	0.446	0.018	0.909	0.187	0.469	0.005
4.	Betullinic acid	0.018	0.582	0.027	0.933	0.183	0.832	0.004
5.	Oleanolic acid	0.013	0.295	0.026	0.883	0.216	0.823	0.012
6.	Fulvoplumierin	0.977	0.89	0.624	0.19	0.423	0.764	0.296
7.	Arjunolic acid	0.009	0.275	0.007	0.822	0.072	0.4	0.003
8.	Isoplumericin	0.704	0.753	0.28	0.375	0.107	0.021	0.029
9.	Plumieride	0.019	0.115	0.023	0.154	0.004	0.024	0.005
10.	Allamandin	0.027	0.969	0.036	0.736	0.011	0.014	0.008
11.	Lignan	0.067	0.985	0.049	0.93	0.04	0.821	0.022
12.	2,5-Dimethoxy-p-benzoquinone	0.979	0.932	0.782	0.79	0.196	0.445	0.564
13.	2,6-Dimethoxy-p-benzoquinone	0.932	0.896	0.572	0.758	0.116	0.129	0.159

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

Sr. No.	Ligand	CL	T1/2
1.	Standard Scopolamine	14.043	0.197
2.	Lepeol	4.161	0.151
3.	Ursolic acid	3.538	0.07
4.	Betullinic acid	2.431	0.27
5.	Oleanolic acid	3.025	0.073
6.	Fulvoplumierin	4.385	0.595
7.	Arjunolic acid	1.819	0.434
8.	Isoplumericin	11.929	0.316
9.	Plumieride	1.714	0.874
10.	Allamandin	10.487	0.484
11.	Lignan	6.756	0.742
12.	2,5-Dimethoxy-p-benzoquinone	5.731	0.795
13.	2,6-Dimethoxy-p-benzoquinone	5.793	0.83

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

Sr. No.	Ligand	Carcinogenicity	Skin Sensitization	Acute Aquatic Toxicity	Toxicophores
1.	Standard Scopolamine	0.115	2	2	2
2.	Lepeol	0.002	0	1	0
3.	Ursolic acid	0.085	0	1	0
4.	Betullinic acid	0.008	0	1	0

5.	Oleanolic acid	0.122	0	1	0
6.	Fulvoplumierin	0.895	2	0	1
7.	Arjunolic acid	0.044	0	1	0
8.	Isoplumericin	0.943	3	5	1
9.	Plumieride	0.949	2	5	1
10.	Allamandin	0.413	3	6	2
11.	Lignan	0.014	4	1	2
12.	2,5-Dimethoxy-p-benzoquinone	0.824	4	3	2
13.	2,6-Dimethoxy-p-benzoquinone	0.835	0	3	2

4. CONCLUSION

According to the study, Scopolamine has a binding affinity of **-7.4 kcal/mol**, while Lepeol's binding affinity for chemical constituents obtained naturally is **-9.6 kcal/mol**. This means that Lepeol has the best interaction with the receptor for Alzheimer's disease (AD), which has the receptor code **PDB ID:5UOG**. Based on molecular docking, ADMET prediction, and interactions with active sites, this medication is utilized as a treatment for Alzheimer's disease (AD). By evaluating the molecule's effectiveness in targeting AD receptors, we were able to confirm this.

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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