

In-silico docking analysis of phytochemicals from mimosa pudica l. Leaves as an antiviral agent against herpes simplex virus type I

Suresh Kumar Gopal^{1*}, Manivannan Rangasamy¹, Nivetha Balasubramaniam²

Abstract

The Herpes Simplex Virus (HSV) infects nearly 85 percent of the world population. Herpes simplex virus infections have been identified in the medical literature for decades, but the drugs currently available for therapy are mostly ineffective, and poor oral bioavailability plays an important role in treatment inefficiency. The specifics of Herpes virus type 1 inhibition are still not fully comprehended. Herpes Simplex Virus (HSV -1) mainly infects the oral and genital mucosa in humans. The purpose of this study is to evaluate the antiviral activity of bioactive compounds present in Mimosa pudica leaves by using computational studies. The structure of bioactive Compounds present in Mimosa pudica leaves has been retrieved from the available repositories (PubChem). The 3D target protein structure selected for the analysis was the Thymidine Kinase (TK) of ID 4OQL retrieved from PDB. The docking study was carried out using Autodock Vina and the interactions were observed using Discovery Studio 3.5 Visualizer. The compound Oreintin and Isovitexin had considerable docking among the compounds tested. The Oreintin displays the best docking score (-7.9 KCal/mol) with 3 hydrogen bond numbers having interactions with the residues SER 254, ARG320, LYS 317 with bond length 2.76, 2.66, 3.01 Å, likewise, Isovitexin shows a docking score of (-7.7 KCal/mol) with 3 hydrogen bonds interacting with residues THR 360, GLY 253, TRP 255 with a bond length of 1.86, 2.81, 2.17 Å, respectively. From ancient times, plants are highly important for human health concerns. Recent developments in scientific technology contribute to the discovery of concepts that underlie the ability to cure different diseases. Future aspects of the analysis are the success of high-throughput virtual screening of several plant compounds and the production of a significant pharmacophore lead or an effective drug.

Keywords: Mimosa Pudica, HSV-1, Thymidine kinase, Traditional medicine, Molecular Docking studies.

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1. Introduction

Coenzyme Q10 (CoQ10) is a compound that is available Herpes Simplex Virus (HSV) mainly infects the oral and genital mucosa caused by HSV type 1 (HSV-1) and HSV type 2 (HSV-2) respectively. Even the infection involves a diverse appearance of the central nervous system (CNS) (1). An estimated 3.7 billion people under the age of 50, or 67 percent of the population, were diagnosed with HSV-1 in 2012. Estimated infection prevalence was highest in Africa (87 percent) and lowest in the Americas (40-50 percent). In terms of genital HSV-1 infection, 140 million people aged 15-49 years were reported to have genital HSV-1 infection worldwide in 2012, but prevalence differed significantly from region

to region. Most genital HSV-1 infections are found in Europe and the West Pacific of the Americas, where HSV-1 tends to be acquired well into adulthood (2). The global burden of HSV-2 infection was also found high threatening 400 million people with genital ulcer disease, HIV acquisition, and transmission to neonates (2). Although neonatal infections are rare, it is estimated 10 out of every 100,000 births globally lead to lasting neurologic disability or death. However, antiviral therapy with acyclovir (ACV) has lowered the death risk significantly, and morbidity remains high (1). The extent of infection varies mainly from cold sores to brain diseases such as encephalitis and distinct as both lytic and latent (3). The lytic process

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gives rise to immediate symptoms while the latter remains still. Acyclovir therapy also faces a resistance problem and recently it was found that resistance to ACV in HSV-1 was due to mutations in the thymidine kinase and/or DNA polymerase genes (4). The biological antiviral activity of triazoloquinazolines against HSV-1 and HSV-2 using molecular docking studies was studied (5). The protein was mainly expressed in the immediate-early genes5 and targeted a variety of proteinases (5). Thymidine kinase was selected in the present study and docking analysis was performed for the compounds in *Mimosa pudica*.

Traditional medicine currently has the very important task of treating about 75-80% of the world's population and hence the WHO's goal is to boost its efficiency and efficacy (6). Modern medicine today in many countries has dislodged plants with many synthetic products, but we must also emphasize that approximately 30% of pharmaceutical formulations are obtained directly or indirectly from plants (7). The plants are typically set as sources of therapeutic agents based on the following parameters. They are intended to isolate bioactive compounds, to create semi-synthesis bioactive compounds, to have higher activity and/or lower toxicity, to use agents as pharmacological tools, and finally to use the whole plant or part of it as a herbal remedy (8). Up to now, only about 6% of plants have been tested for their biological activity and 15% have been registered for phytochemistry. There is also the assumption that bioactive compounds obtained from plant sources should be less harmful to humans (9).

The enzyme, thymidine kinase (TK), plays an important role in HSV-1 virus DNA synthesis. TK gene mutation results in decreased viral pathogenicity. To the credit, the latent infection of sensory ganglion neurons has its importance (10). Thus in the present analysis, TK was chosen as the antiviral target.

Mimosa Pudica L. commonly referred to as 'Lajjabati' belonging to the Fabaceae family, is a strong strangling prostrate shrubby plant with compound leaves, touch-sensitive, spinous stipulations, and globose pink flower heads (11)(12)(13). It originates in South America and is naturalized all over India's tropical and subtropical regions. The plant is considered diuretic, antispasmodic, and astringent. The leaves and roots are used for pile and fistula care. Leaf paste is used in hydrocele. Cotton impregnated with leaf juice is used for sinus dressing. The plant is also useful for treating sore gums and is used as a purifier for blood (14). It's

also used to treat children's seizures. The ethanolic extract of *Mimosa pudica* demonstrated nootropic (cognition enhancement) activity in Wistar Albino Rats and also antihelmintic activity (15). Various studies have indicated that this plant has therapeutic activities such as urolithiasis, ovulation, biocidal, antidepressant, estrogenic and antiestrogenic activity, anti-implantation and antiestrogenic activity, estrous cycle and ovulation effects, hyperglycemic activity, anticonvulsant activity, hyaluronidase, and protease activity(16-20).

Various literature indicated that *Mimosa pudica* contain compounds such as Crocetin, Mimosine, Thiamine (19), Turgorin (21), Isorientin, Orientin, Isovitexin, Vitexin (22), D-pinitol (23), and Quercetin (24). This research was aimed at defining the anti-viral role of *Mimosa pudica* by studying the In Silico molecular docking to evaluate the novel compound with the inhibitory action against the Thymidine Kinase enzyme. Analyzing the docking involves predicting ligand conformation and orientation (or posing) within a specified binding position..

2. MATERIALS AND METHODS:

Online databases such as PubMed, PubChem, and PDB have been used in bioinformatics. PubMed database is structured to provide access to scientific journal citations. The PubChem database contains information on the small molecules 'biological activities. PubChem also offers a search tool for the similarity of a rapid chemical structure.

Preparation of Protein:

The dimensional structure of Thymidine Kinase (TK) (Protein Data Bank [PDB] ID - 4OQL) was retrieved using Protein Data Bank which could act as a target molecule for molecular docking. The structure was viewed using Swiss - PDB Viewer to form a better understanding of the molecule to use it as a drug target.

Selection of Phytochemicals:

From the literature review, all compounds, Crocetin, Mimosine, Thiamin, Turgorin, Isorientin, Orientin, Isovitexin, Vitexin, D-pinitol, and Quercetin in Table 1 are downloaded from PubChem in 2D-SDF format.

ADME/T Properties:

The properties of ADME (absorption,



distribution, metabolism, and excretion) were determined using smile notation in the Swiss ADME Web-based tool (25). This website enables the computation of physicochemical descriptors as well as the prediction of ADME parameters, pharmacokinetic properties, drug-like behavior, and the friendliness of one or more small molecules in medicinal chemistry to help drug discovery. The toxicity was measured using the PROTOX sever (26).

Drug-likeness prediction:

Drug-likeness is the term used in drug design, to predict the molecular structure before synthesizing and analyzing the molecular structure. A drug-like molecule has properties including solubility (Log P), potency, Lipophilic strength, number of donors of hydrogen bonds vs. alkyl sidechains, molecular weight, and mutagenic and carcinogenic properties. Molsoft online program predicts drug-likeness. The drug-likeness model score will be obtained from the compounds. The score should be between 0-1 for a molecule to be deemed to be drug-likeness property.

Docking and Visualization:

The 9 phytochemicals were docked with the target protein Thymidine kinase (HSV-1). The docking was carried out using the AutoDock Vina. Docking between the target protein receptor and phytochemicals was visualized using AutoDock Vina 1.5.6 and Discovery Studio Visualizer 3.5.

3. RESULTS:

Molecular Docking

AutoDockVina is an open-source program for drug discovery, molecular docking, and virtual screening, providing multicore capacity, high performance, and improved precision and ease of use molecular docking experiments were conducted to investigate the binding affinity of the selected phytochemicals. The compound Orientin and Isoviteixin received the highest score for docking with both the HSV-1 target had considerable docking among the compounds tested.

The Orientin displays docking score (-7.9 KCal/mol) with 2 hydrogen bond numbers showing interactions with the residues ARG 320 with bond length 2.65 Å. Isoviteixin displays a docking score of (-7.7 KCal/mol) with hydrogen bonds interacting with residues THR 360, GLY 253, TRP 255 with a bond length

of 1.86, 2.81, 2.17 Å, respectively. The docking results are shown in Fig(1-6) and the interaction pattern of the remaining Phytochemical and compiled results are shown in Table 1.

Using Swiss ADME, a free web tool, the ADMET properties for the compounds were calculated. The toxicity was measured using the web-based method PROTOX. Toxic doses are mostly given in mg/kg of body weight as LD50 values. The drug-likeness model scores of compounds were obtained from online molsoft software The ADME properties, the molecular properties, the bioavailability scores, toxicity analysis, and drug-likeness scores of phytochemical of *Mimosa pudica* are given in Tables 2-8.

4. DISCUSSION

A large number of medicinal plants have been shown to have beneficial therapeutic potential and to serve as a rich source of secondary metabolites for a variety of biological activities. These secondary metabolites may serve as lead molecules. Seven of the thirteen phytochemicals (ligands) followed Lipinski's law of five. Using the PROTOX toxicity prediction method, the toxicity of phytochemicals meeting the properties of Lipinski was calculated. Higher lipophilicity compounds were better absorbed through the intestine. Low molecular weight molecules (< 500) are rapidly transported, diffused, and absorbed compared to large molecules. The absorption and excretion rates are also dependent on molecular weight (MW).

The higher MW allows for higher absorption and lower bile excretion. A significant element in the action of therapeutic drugs is the molecular weight. If it rises above those thresholds, which in effect influence the drug action, the bulkiness of the compounds also increases. A free web tool, SwissADME, has been used to test the ADMET properties of the compounds. The average number of hydrogen bonds donated is in the 3-8 range. The number of hydrogen bonds that would be approved is estimated at 3-11. The number of violations of Lipinski's rule of five is allowed is 0-2. Drug Likeness test was checked for the phytochemicals by using Online Molsoft application Software. The Drug-Likeness score should be between 0- 1for a compound to be like a drug. All Nine compounds are within the spectrum here and can be regarded as a drug.





FIGURE 1: Orientin Docked to the Active Site Of Thymidine Kinase (TK).

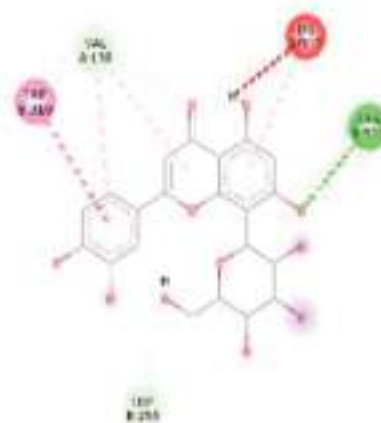


FIGURE 4: Ligand Interaction Map of Orientin

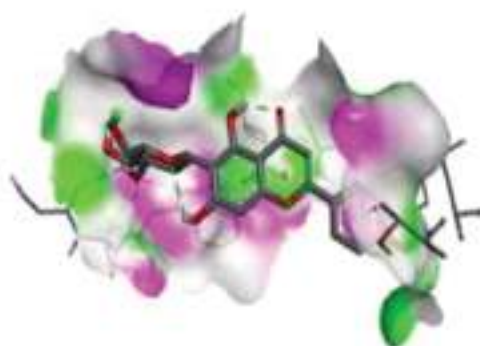


FIGURE 2: Isovitexin Docked to the Active Site Of Thymidine Kinase (TK)

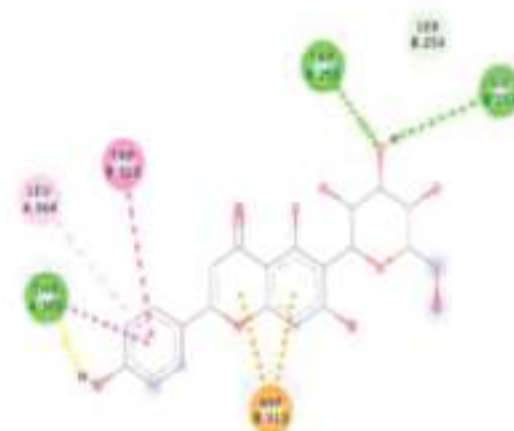


FIGURE 5: Ligand Interaction Map Of Isovitexin

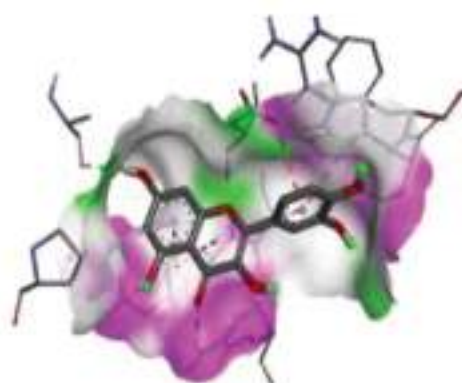


FIGURE 3: Quercetin docked to the Active Site of Thymidine Kinase (TK)



FIGURE 6: Ligand Interaction Map of Quercetin

TABLE 1: Docking results of Phytochemical Of Mimosa Pudica leaves

S.No	Compound Name	Docking score Kcal/mol	No. of Bonds	Interacting Residues	Bond Length (Å)
1	Orientin	-7.9	3	ARG320 (O-H) TRP 255(C-H) LYS 317(O-H)	2.66 2.88 3.01
2	Isovitexin	-7.7	3	THR 360(O-H) GLY 253 (O-H) TRP 255 (O-H)	1.86 2.81 2.17
3	Quercetin	-7.6	4	ALA137 (O-H) LYS317(O-H) TRP 255 (O-H) ARG 320 (O-H)	2.46 2.01 2.84 2.42
4	Crocetin	-7.1	1	ARG 366 (O-H)	2.18
5	Turgorin	-7.1	4	ASP 313(O-H) VAL 138(O-H) HIS 142(O-H) ASP 363(O-H)	1.90 2.09 2.39 2.14
6	Vitexin	-7.0	1	ARG 320(O-H)	2.64
7	Thiamine	-6.4	2	ASN 99(O-H) GLY 92(O-H)	2.88 2.37
8	D-pinitol	-5.3	2	SER 193 (O-H)	2.98 2.07
9	Mimosine	-5.1	1	THR 122 (O-H)	1.82

TABLE 2: Lipophilicity Of Phytochemicals of Mimosa Pudica leaves

S. no.	Phytochemical	LogPo/w (iLOGP)	Log Po/w (XLOGP3)	Log Po/w (WLOGP)	Log Po/w (MLOGP)	Log Po/w (SILICOS-IT)	Consensus Log Po/w
1.	Crocetin	3.33	5.41	4.61	3.52	4.16	4.21
2.	Mimosine	0.69	-4.36	-1.03	-4.13	-0.98	-1.96
3.	Thiamine	-1.60	1.02	0.62	0.05	2.54	0.53
4.	Turgorin	-0.80	-2.36	-1.46	-2.70	-3.34	-2.21
5.	Orientin	1.27	-0.15	-0.53	-2.51	-0.14	-0.41
6.	Isovitexin	1.94	0.21	-0.23	-2.02	0.33	0.05
7.	Vitexin	1.38	0.21	-0.23	-2.02	0.33	-0.07
8.	D-pinitol	0.36	-3.17	-3.18	-2.81	-2.50	-2.26
9.	Quercetin	1.63	1.54	1.99	-0.56	1.54	1.23



TABLE 3: Water Solubility of Phytochemicals of Mimosa Pudica leaves

S. No.	Phytochemical	Log S (ESOL)	Solubility	Class	Log S (AII)	Solubility	Class	Log S (SILICO-IT)	Class
1	Crocetin	-4.76	5.75e-03 mg/ml; 1.75e-05 mol/l	Moderately soluble	-6.73	6.09e-05 mg/ml; 1.85e-07 mol/l	Poorly soluble	-0.78	Soluble
2	Mimosine	1.56	7.18e+03 mg/ml; 3.62e+01 mol/l	Highly soluble	2.76	1.13e+05 mg/ml; 5.71e+02 mol/l	Highly soluble	-0.01	Soluble
3	Thiamine	-2.32	1.28e+00 mg/ml; 4.83e-03 mol/l	Soluble	-2.80	4.24e-01 mg/ml; 1.60e-03 mol/l	Soluble	-3.30	Soluble
4	Turgorin	0.67	8.76e+01 mg/ml; 2.13e-01 mol/l	Very soluble	-1.97	4.42e+00 mg/ml; 1.08e-02 mol/l	Very soluble	1.98	Soluble
5	Orientin	-2.70	9.00e-01 mg/ml; 2.01e-03 mol/l	Soluble	-3.62	1.07e-01 mg/ml; 2.39e-04 mol/l	Soluble	-1.79	Soluble
6	Isovitexin	-2.84	6.29e-01 mg/ml; 1.46e-03 mol/l	Soluble	-3.57	1.16e-01 mg/ml; 2.68e-04 mol/l	Soluble	-2.38	Soluble
7	Vitexin	-2.84	6.29e-01 mg/ml; 1.46e-03 mol/l	Soluble	-3.57	1.16e-01 mg/ml; 2.68e-04 mol/l	Soluble	-2.38	Soluble
8	D-pinitol	1.02	2.03e+03 mg/ml; 1.05e+01 mol/l	Highly soluble	1.42	5.11e+03 mg/ml; 2.63e+01 mol/l	Highly soluble	2.58	Soluble
9	Quercetin	-3.16	2.11e-01 mg/ml; 6.98e-04 mol/l	Soluble	-3.91	3.74e-02 mg/ml; 1.24e-04 mol/l	Soluble	-3.24	Soluble

TABLE 4: Pharmacokinetics of Phytochemicals of Mimosa Pudica leaves

S. no.	Phytochemical	GI absorption	BBB permeant	P-gp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP2D6 inhibitor
1.	Crocetin	High	No	No	No	Yes	Yes	No	No
2.	Mimosine	High	No	No	No	No	No	No	No
3.	Thiamine	High	No	Yes	No	No	No	No	No
4.	Turgorin	Low	No	No	No	No	No	No	No
5.	Orientin	Low	No	No	No	No	No	No	No
6.	Isovitexin	Low	No	No	No	No	No	No	No
7.	Vitexin	Low	No	No	No	No	No	No	No
8.	D-pinitol	Low	No	Yes	No	No	No	No	No
9.	Quercetin	High	No	No	Yes	No	No	Yes	Yes



TABLE 5: Drug likeness of Phytochemicals of Mimosa Pudica leaves

S. no.	Phytochemical	Lipinski	Ghose	Veber	Egan	Muegge	Bioavailability Score
1	Crocin	Yes; 0 violation	Yes	Yes	Yes	No; 1 violation: XLOGP3>5	0.56
2	Mimosine	Yes; 0 violation	No; 1 violation: WLOGP<-0.4	Yes	Yes	No; 2 violations: MW<200, XLOGP3<-2	0.55
3	Thiamine	Yes; 0 violation	Yes	Yes	Yes	Yes	0.55
4	Turgorin	No; 2 violations: NorO>10, NHorOH>5	No; 1 violation: WLOGP<-0.4	No; 1 violation: TPSA>140	No; 1 violation: TPSA>131.6	No; 4 violations: XLOGP3<-2, TPSA>150, H-acc>10, H-don>5	0.11
5	Orientin	No; 2 violations: NorO>10, NHorOH>5	No; 1 violation: WLOGP<-0.4	No; 1 violation: TPSA>140	No; 1 violation: TPSA>131.6	No; 3 violations: TPSA>150, H-acc>10, H-don>5	0.17
6	Isovitexin	Yes; 1 violation: NHorOH>5	Yes	No; 1 violation: TPSA>140	No; 1 violation: TPSA>131.6	No; 2 violations: TPSA>150, H-don>5	0.55
7	Vitexin	Yes; 1 violation: NHorOH>5	Yes	No; 1 violation: TPSA>140	No; 1 violation: TPSA>131.6	No; 2 violations: TPSA>150, H-don>5	0.55
8	D-pinitol	Yes; 0 violation	No; 1 violation: WLOGP<-0.4	Yes	Yes	No; 2 violations: MW<200, XLOGP3<-2	0.55
9	Quercetin	Yes; 0 violation	Yes	Yes	Yes	Yes	0.55

TABLE 6: Molecular properties of Phytochemicals of Mimosa Pudica leaves

S. no.	Phyto-chemical	miLogP	TPSA	natoms	MW	nON	nOHNH	N violations	nrothb	volume
1.	Crocin	4.63	74.60	24	328.41	4	2	0	8	324.80
2.	Mimosine	-4.16	105.56	14	198.18	6	4	0	3	168.33
3.	Thiamine	-3.45	75.92	18	265.36	5	3	0	4	239.76
4.	Turgorin	-4.61	223.34	27	411.32	13	6	2	6	304.89
5.	orientin	0.03	201.27	32	448.38	11	8	2	3	363.22
6.	Isovitexin	0.52	181.04	31	432.38	10	7	1	3	355.20
7.	Vitexin	0.52	181.04	31	432.38	10	7	1	3	355.20
8.	D-pinitol	-1.99	110.37	13	194.18	6	5	0	1	168.39
9.	Quercetin	1.68	131.35	22	302.24	7	5	0	1	240.08



TABLE 7: Bioavailability scores of Phytochemicals of Mimosa Pudica leaves

S. no.	Phyto-chemical	GPCR ligand	Ion chan-nel modu-lator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
1	Croctin	0.13	0.19	-0.01	0.68	-0.04	0.40
2	Mimosine	-0.39	0.09	-0.44	-0.51	-0.07	0.42
3	Thiamine	0.26	0.01	-0.37	-1.72	-0.64	1.12
4	Turgorin	0.03	-0.10	-0.15	0.09	0.12	0.44
5	orientin	0.12	-0.14	0.20	0.20	0.01	0.45
6	Isovitexin	0.12	0.02	0.15	0.23	0.04	0.47
7	Vitexin	0.13	-0.14	0.19	0.23	0.03	0.46
8	D-pinitol	-0.54	-0.08	-0.69	-0.55	-0.51	-0.05
9	Quercetin	-0.06	-0.19	0.28	0.36	-0.25	0.28

TABLE 8: Oral toxicity prediction results of Phytochemicals of Mimosa Pudica leaves

S. no.	Phytochemical	Predicted LD 50	Predicted toxicity class	Average similarity	Prediction accuracy
1	Croctin	4300mg/kg	5	68.97%	68.07%
2	Mimosine	2000mg/kg	4	53.17%	67.38%
3	Thiamine	3710mg/kg	5	100%	100%
4	Turgorin	3750mg/kg	5	62.51%	68.07%
5	Orientin	1213mg/kg	4	58.25%	67.38%
6	Isovitexin	159mg/kg	3	63.84%	68.07%
7	Vitexin	1213mg/kg	4	58.28%	67.38%
8	D-pinitol	804mg/kg	4	75.9%	69.26%
9	Quercetin	159mg/kg	3	100%	100%

CONCLUSION:

Among those compounds, Orientin and isovitexin were found to have the best binding energy. In particular, we conclude that these two phytochemicals can be used as a valuable treatment for HSV-1 infection. In the future, research needs to focus on screening large numbers of antiviral compounds from different plants to find an effective drug candidate.

Compliance with Ethical Standards

The authors declare that they have no conflict of interest. This article does not contain any studies involving animals or human participants performed by any of the authors

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